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ORIGINAL RESEARCH

Clinical Characteristics and Epidemiological Analysis of Pneumocystis Jirovecii Pneumonia Infection in Kidney Transplant Patients with Trimethoprim-Sulfamethoxazole Dose Reduction Prophylaxis Strategy

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Background: The administration of trimethoprim-sulfamethoxazole (TMP-SMX) for the prophylaxis of Pneumocystis jirovecii pneumonia (PJP) has proven to be highly efficacious in individuals who have undergone kidney transplantation. Nevertheless, the potential for severe adverse reactions associated with this treatment cannot be overlooked, and the determination of an optimal dosage regimen continues to be a matter of investigation. The current study evaluated the effectiveness of low-dose TMP-SMX for PJP prophylaxis in kidney transplant patients and conducted an analysis of the clinical characteristics and epidemiological trends in patients with PJP infection.

Methods: This retrospective analysis studied electronic medical records of 1763 kidney transplant recipients from 2017 to 2020. These patients were initially prescribed a daily half-strength TMP-SMX (40 mg/200 mg), and the efficacy of this regimen was assessed during a follow-up period of 3–51 months.

Results: Under our PJP prevention and adjustment strategy, 24 patients were infected with PJP. The overall morbidity of PJP infection in our study was 1.36%, corroborates with findings from previously published studies. Among these 24 patients, up to 87.5% had their dosage adjusted due to increased creatinine or other adverse reactions, the most frequent dose was daily quarter-strength TMP-SMX (20 mg/100 mg). TMP-SMX prophylaxis successfully postponed and distributed the onset of PJP, with the mean duration from transplantation to the occurrence of PJP being 13.50±7.11 months.

Conclusion: Daily administration of half-strength TMP-SMX can effectively prevent PJP, and prolonging prophylaxis with this medication may potentially reduce the incidence of infection.

Keywords: efficacy, kidney transplant recipients, Pneumocystis jirovecii pneumonia, trimethoprim-sulfamethoxazole

Introduction

Pneumocystis jirovecii pneumonia (PJP) is a serious, potentially fatal complication, with high incidence among HIV, cancer, or transplant recipients. Even with active antibiotic treatment, the mortality rate associated with PJP can increase to as high as 50%.[1,2] Before the adoption of routine prophylaxis, 5% to 15% of solid organ transplant patients were at risk of developing PJP following transplantation.[3,4] Prophylaxis of PJP with trimethoprim-sulfamethoxazole (TMP-SMX) has proven to be exceptionally effective in kidney transplant recipients (KTRs).[5] The recommended dosing for

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TMP-SMX spans from single-strength (80 mg/400 mg) daily to double-strength (160 mg/800 mg) thrice weekly, with the advised duration of PJP prophylaxis extending from six to twelve months.[6]

TMP-SMX associates with numerous adverse drug reaction, such as leukopenia, absolute neutropenia, renal toxicity, thrombocytopenia, anemia, and hepatitis. These adverse events are often poorly tolerated and may lead to the discontinuation of treatment. For patients who cannot tolerate TMP-SMX, aerosolized pentamidine, dapsone, or atovaquone offer viable prophylactic alternatives for the prevention of PJP. However, it should be noted that access to these medications in China remains limited. TMP-SMX remains the preferred prophylactic agent for preventing PJP and is widely used in clinical settings. Thus, post-transplant management requires a balance between the prevention of PJP and the mitigation of adverse reactions associated with TMP-SMX.

Studies have confirmed that six months of daily single-strength TMP-SMX prophylaxis was more efficacious than thrice weekly double-strength TMP-SMX.[7] Meanwhile, in patients prescribed daily single-strength TMP-SMX, dose reductions were commonly observed, with nearly 50% of patients having their dosing regimen adjusted to single-strength, thrice weekly.[8] We investigated seven hospitals in China and found that the prevention strategies of each hospital were different. The dosage of TMP-SMX varies from quarter-strength (20 mg/100 mg) daily to a double-strength (160 mg/800 mg) taken three times weekly. Most hospitals have adjusted the preventive dose for kidney transplant patients, but the lowest effective dose has not yet been determined.

In the absence of data from randomized controlled trials, the ideal dosage of TMP-SMX for PJP prophylaxis is yet to be determined. This study was designed to evaluate the effectiveness of low-dose TMP-SMX in preventing PJP among kidney transplant recipients and conducted an analysis of the clinical characteristics and epidemiological trends in patients with PJP infection.

Methods

Study Design and Patient Population

We conducted a retrospective analysis of electronic medical records for patients who underwent transplantation from January 1, 2017 to December 30, 2020. All kidneys were voluntarily donated with written informed consent, strictly adhering to the ethical guidelines outlined in the Declaration of Istanbul. These patients were initially prescribed a daily half-strength TMP-SMX (40 mg/200 mg) during their first hospital admission, with a planned continuation of at least six months post-transplantation for PJP prophylaxis. When the creatinine increased by 10%, the dose was reduced to a daily quarter-strength and extend the prevention time when necessary. If further reduction was deemed necessary, stop entirely. In the event that a patient encountered rejection reactions, modifications to the immunotherapy protocol were implemented, and preventative measures for PJP were reinstituted to minimize any conceivable hazards.

All the kidney recipients received rabbit-antihuman-thymocyteimmunoglobulin or basiliximab. The immunotherapy regimen predominantly comprises tacrolimus or cyclosporine, along with mycophenolate mofetil and adjunctive hormone therapy. The target trough concentration values for tacrolimus were maintained between 8–10 ng/mL during the first postoperative month, between 6–8 ng/mL from the 1st to the 6th month, and between 5–7 ng/mL after 6 months. The cyclosporine trough concentration was maintained at 120–200 ng/mL.

Data Collection

The study encompassed 1763 patients who received their initial kidney transplants at our institution, and the observation period for these patients was 3–51 months.

To calculate the incidence of PJP infection, we screened PJP infected patients who were hospitalized in the First Hospital of Zhejiang University from January 1, 2017 to March 31, 2021 in the system. The search strategy included keywords such as “Pneumocystis carinii, Pneumocystis pneumoniae, Yersinia pneumoniae, PJP, PCP, and severe pneumonia” in the discharge diagnosis, and a total of 96 patients were retrieved. Among them, 39 cases were duplicate patients, 21 cases were non kidney transplant patients such as AIDS, 5 cases were not in the observation period, and 7 cases were not transplanted in our hospital. After excluding these patients, a total of 24 PJP infection cases were obtained during the observation period (Figure 1).

The diagnosis of PJP was definitively established either through the detection of pneumocystis cysts or trophozoites in bronchoalveolar lavage fluid, or by utilizing a combination of methods including next-generation sequencing analysis of bronchoalveolar lavage fluid or blood samples, along with radiographic confirmation via computed tomography (CT) scans. Additionally, measurements of blood beta-D-glucan levels were incorporated into the comprehensive diagnostic workflow to ensure accurate diagnosis.

We mainly use electronic case systems to search for the basic patient information and treatment strategies, we can also supplement other information through phone calls or face-to-face interviews.

Statistical Analysis

Data were expressed as the mean ± SD or median (interquartile range) for continuous variables and counts with percentages for categorical variables. All analyses were performed using SPSS 26.

Results

Patient Inclusion

A total of 1763 patients who received their primary kidney transplant at our hospital was evaluated for eligibility according to the inclusion criteria. The process of inclusion and exclusion is depicted in Figure 1. Finally, 24 patients were found to be eligible and were included in the analysis. In terms of gender composition, 15 cases linked to male, which accounted for 62.50% of all cases, and the average age of PJP infected patients was 37.63. Tacrolimus was the main treatment to maintain immunosuppressive strategy and prevent allograft rejection. The demographic characteristics of the participants are detailed in Table 1.

Prevalence of PJP

In this research, 24 patients were observed to have PJP infection during the study period. The prevalence of PJP infection was 1.36% (24/1763).

Among these patients, a total of 5 patients stopped TMP-SMX treatment. Meanwhile, the most frequent dose was daily quarter-strength TMP-SMX (20mg/100mg), accounting for 66.67% of all patients (see Table 2).

Temporal Characteristics of PJP Infected Patients

Under the current prevention and adjustment strategies, the 1-year incidence of PJP infection after transplantation was 0.68% (12/1763), and the incidence of PJP infection occurring within the 12 months to 24 months was 0.62% (11/1763) (see Table 3). The mean time between the onset of PJP and transplantation was 13.50±7.11 months, indicating that taking

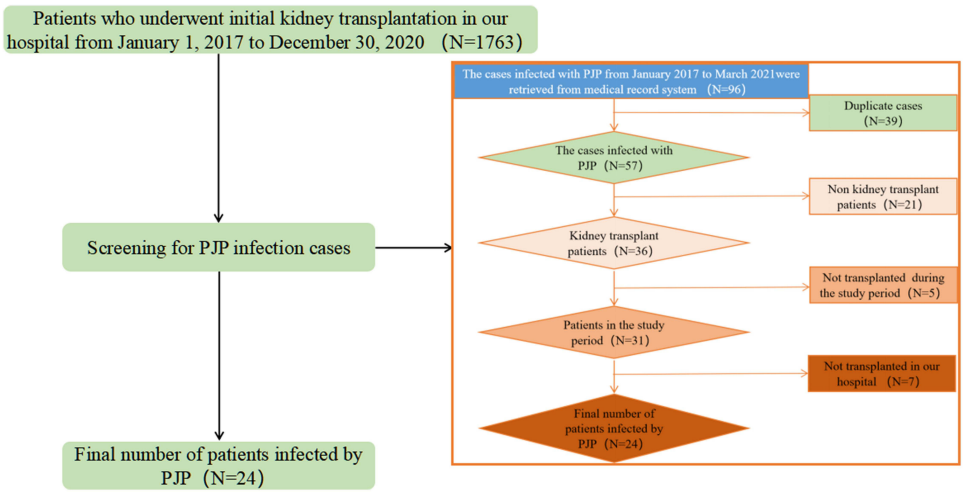

Figure 1 Case screening flow chart.

Table 1 Demographic Characteristics of PJP Infected Patients

Characteristic	Patients (n=24)
Gender, male (n, %)	15 (62.50)
Gender, female (n, %)	9 (37.50)
Age, median (IQR)	35 (29, 47)
Height, median (IQR), (cm)	164.50 (158.50, 170.00)
Weight, median (IQR), (kg)	52.90 (47.25, 58.00)
Body mass index, median (IQR)	19.34 (18.20, 21.32)
Preoperative dialysis mode (n,%)	
Hemodialysis /peritoneoclysis	21 (87.50%)
Other	3(12.50%)
History of CMV infection (n,%)	6(25.00%)
Immune rejection (n,%)	4(16.67%)
Induction drug after kidney transplantation (n,%)	
Basiliximab	14 (58.33%)
Rabbit anti-human thymocyte immunoglobulin	9(37.50%)
Combination	1(4.17%)
Immunosuppressive strategy (n,%)	
Tacrolimus	22 (91.67%)
Ciclosporin	2(8.33%)
Trough level of tacrolimus, median (IQR), (ng/mL)	6.40 (4.63, 8.18)
Serum creatinine, median (IQR), umol/l	336 (113, 531)
eGFR, median (IQR), mL/min/1.73m^2	20.30 (11.84, 63.74)

Abbreviations: IQR, interquartile range; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate.

Table 2 TMP-SMX Dosage in Patients with PJP Infection

Characteristic	Patients (n=24)
The prophylactic dose of TMP-SMX (n,%)	
Daily half-strength (40mg/200mg)	3(12.50%)
Daily quarter-strength (20mg/100mg)	16(66.67%)
Stopped entirely	5(20.83%)
Prophylactic Duration, median (IQR), months	10 (3, 12)
Total prophylactic dose of TMP-SMX, median (IQR), tablets	48.75 (11.38, 90.00)

Abbreviations: IQR, interquartile range; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 3 Onset Time of PJP

Onset Time (Months)	Patients (n=24)	Percent (%)
≤6	6	25.00
6–12	6	25.00
12–18	5	20.83
18–24	6	25.00
≥24	1	4.17

TMP-SMX prophylaxis delayed the onset of PJP. Among the patients with PJP, 4 patients had previous rejection, and their time to transplantation was 9, 17, 22 and 22 months, respectively. Excluding these 4 patients, the mean time between the onset of PJP and transplantation was 12.70±7.16 months. The cumulative incidence of PJP was showed in Figure 2.

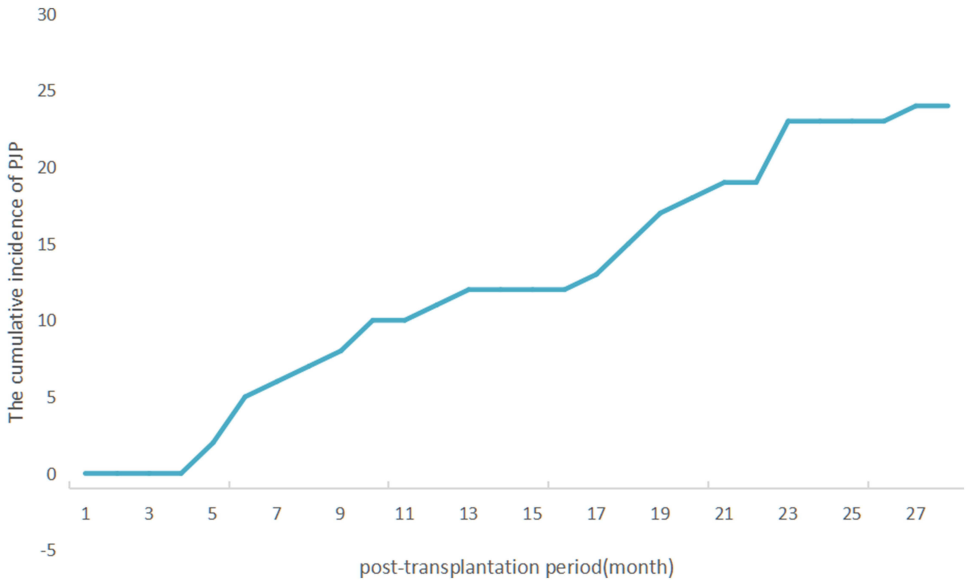

Figure 2 The number of patients who developed PJP infections post-transplantation.

Outcome of PJP

TMP-SMX is the primary treatment for PJP, and was used in all 24 cases, including 16 cases of TMP-SMX alone and 8 cases of combined caspofungin. Among them, 23 patients were discharged from hospital after recovery, and 1 patient who received combined treatment was died (see Table 4).

Discussion

To our knowledge, this study represents the first evaluation of the efficacy of daily half-strength TMP-SMX for PJP prophylaxis in kidney transplant patients, as well as an analysis of the clinical characteristics and epidemiological trends in patients with PJP infection.

Pneumocystis infection was initially described in human lungs in 1942,[9] and the risk of infection is higher in transplant patients. Since its introduction in 1968, TMP-SMX has been established as an effective prophylactic agent against PJP, as evidenced by a large randomized trial in HIV-infected patients. The trial showed that administering a double-strength TMP-SMX daily or three times weekly can prevent PJP.[10,11] However, discontinuation rates due to adverse effects were notable, reaching up to 10% in the thrice-weekly group and 20% in the daily-group, after which PJP occurred. The discontinuation of the treatment was attributed to adverse events such as acute kidney injury, leukopenia, and gastrointestinal disturbances.[12–14] Therefore, the focus of research has shifted towards exploring ways to minimize the occurrence of adverse events and determining whether low dosages of TMP-SMX remain effective in preventing PJP.

Some studies favored administering a double-strength TMP-SMX (160mg /800mg) once daily, while others proposed administering the same double-strength TMP-SMX orally twice daily or three times weekly.[15,16] Clearly, there was a divergence in research findings regarding the optimal dosing regimen.

Previous research has established that daily administration of single-strength TMP-SMX effectively prevents PJP within the first year following transplantation, but associated with significant side effect. Nearly half of the kidney

Table 4 The Treatment and Outcome of PJP

Treatment	Patients (n=24)	Outcome
TMP-SMX alone	16	recovery
TMP-SMX combined caspofungin	8	7 patients recovered and 1 failed

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

transplant recipients required a dose reduction of TMP-SMX, primarily because of hyperkalemia and leukopenia.[8] Moreover, 45 patients presented with an estimated glomerular filtration rate (eGFR) less than 30mL/min/1.73m². In a retrospective observational study including 1469 kidney transplant recipients, it was found that, compared to the non-prophylaxis group, both quarter-strength TMP-SMX (20mg/100 mg) administered daily and every other day significantly reduced the occurrence of PJP, all the while maintaining a positive safety profile. Nevertheless, it's crucial to mention that this study solely concentrated on the initial six months after kidney transplantation, emphasizing the necessity for long-term follow-up extending beyond this six-month period.[17]

In our study, oral administration of half-strength TMP-SMX (40 mg/200 mg) was prescribed daily, and the efficacy of this regimen was assessed during a follow-up period of 3–51 months. If initiating treatment with a half-strength TMP-SMX daily can maintain its efficacy in preventing PJP, this reduced dosage approach may yield benefits for both clinicians and patients.

Now with widespread use of prophylaxis, the incidence of post-transplant complications is reported to vary between 0.3% and 2.5%.[18–21] Under our PJP prevention and adjustment strategy, a total of 1763 kidney transplant patients were enrolled in the study from 2017 to 2020. All patients were treated with a daily half-strength TMP-SMX. During the follow-up period, 24 patients were infected with PJP. The overall morbidity of PJP infection in our study (1.36%) was consistent with previous published study, and half-strength TMP-SMX proved to be effective in preventing PJP.

Among these 24 patients, up to 87.5% had their dosage adjusted due to increased creatinine or other adverse reactions, and 5 patients stopped treatment. Most patients with PJP infection reduced the dose of TMP-SMX to daily quarter-strength during treatment, which may lead to infection, but our current data were limited and not enough to confirm this. Further studies were still needed to confirm the effectiveness of lower doses of TMP-SMX and its association with PJP infection. Among the 24 patients infected with PJP, 23 of them improved after treatment, but one patient died even after combined treatment due to severe illness.

Current guidelines recommend that prophylaxis for PJP should be administered for a duration of 6 to 12 months following transplantation, but patients still have the risk of PJP after the complete prevention process. Most patients with PJP have risk factors for pneumocystis pneumonia. Prolonged preventive measures for patients with risk factors can reduce the incidence of PJP. Goto et al[22] suggested lifelong prevention for kidney transplant recipients to prevent new outbreaks.

PJP usually occurs 3–6 months after kidney transplantation, but in our study, only 25% of patients occurred within six months. In our observation window (average 27 months, the longest 48 months), only 6 cases had PJP within 6 months from the time of transplantation, 12 cases within 1 year, and 1 case occurred more than 24 months. The average time from the occurrence of PJP to transplantation was 13.50±7.11 months, indicating that TMP-SMX prevention delayed the occurrence of PJP, and the occurrence time was scattered.

Our study also revealed that up to 75% of patients developed PJP infection 6 months after transplantation, and we believe that extending the prophylaxis period is necessary, which may reduce the incidence of infection.

Despite establishing an effective prevention program in our study, there are still several limitations to consider. First, it should be noted that the study was conducted at a single center, which may potentially limit the generalizability of the findings. Future multi-center collaborations are necessary to further determine the minimum effective dose of TMP-SMX. Second, the recipients in our study possess significantly lower body mass indexes. As a result, the lower medication doses utilized in our investigation may not be suitable for patients with larger body sizes. Last, while our study focused on assessing the efficacy of the TMP-SMX treatment regimen, it did not comprehensively address important issues related to patient non-adherence, which is a critical factor that can significantly impact the overall effectiveness of the treatment and patient outcomes.

Conclusion

This investigation represents the inaugural study assessing the effectiveness of daily half-strength TMP-SMX for PJP prophylaxis in kidney transplant patients, and the overall morbidity of PJP infection was 1.36%. Among these patients with PJP infection, up to 87.5% had their dosage adjusted due to increased creatinine or other adverse reactions, further studies on the incidence of PJP at lower dose of TMP-SMX are also warranted. Meanwhile, to reduce infection,

transplant patients can extend the prevention time when necessary. These findings may aid in the clinical application of TMP-SMX.

Data Sharing Statement

The datasets generated and/or analyzed during the present study are accessible from the corresponding author, Kuifen Ma, upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (Number: 2018-1083). All procedures involving human participants complied with the ethical standards of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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