Impact of Increased Duration of Trimethoprim-Sulfamethoxazole Prophylaxis for Pneumocystis Pneumonia After Renal Transplant

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended as prophylaxis against Pneumocystis pneumonia (PCP) in renal transplant recipients. The optimal duration of prophylaxis is unknown. Longer duration of prophylaxis may increase the risk of adverse effects. The aim of this retrospective observational cohort study was to assess the impact of increasing duration of TMP-SMX prophylaxis from 3 to 6 months after transplant on drug-resistant urinary tract infection (UTI), hyperkalemia, peripheral blood cytopenias, and incidence of PCP.

Material/Methods: Patients transplanted over a 4.5-year period before and after a change in protocol from 3- to 6-months TMP-SMX prophylaxis in our unit were grouped according to planned duration of prophylaxis, and results were analyzed on an intention-to-treat basis. Baseline characteristics, laboratory values, and all urine microbiology results in the 6 months after transplant were analyzed.

Results: The overall UTI incidence rate was higher in the 3-month (3-m) treatment group than the 6-month (6-m) treatment group (0.52 *vs.* 0.33 UTI per 100 patient days; rate ratio 1.56 [95% CI 1.27–1.95]). However, this was not attributable to TMP-SMX: the incidences were significantly different in months 0–3 but not months 4–6. Twenty-eight multi-resistant UTIs occurred in the 3-m group, but there were none in the 6-m group (p=0.004). There were no significant differences in renal function, serum potassium, or cytopenias during the first 6 months. There were 15 cases of PCP in the 3-m group, 3 cases in the 6-m group, and no cases during prophylaxis.

Conclusions: Extending the duration of TMP-SMX prophylaxis was not associated with change in frequency of UTIs or multi-drug-resistant UTIs, nor was it associated with increased adverse events. TMP-SMX is an effective PCP prophylaxis, and these data support recommendations to extend the duration of prophylaxis after transplant.

MeSH Keywords: Antibiotic Prophylaxis • Drug-Related Side Effects and Adverse Reactions • Kidney Transplantation • *Pneumocystis carinii* • Trimethoprim-Sulfamethoxazole Combination • Urinary Tract Infections

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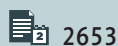
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Background

Pneumocystis pneumonia (PCP) caused by *Pneumocystis jirovecii*, a common fungal pathogen, is a life-threatening complication following renal transplantation. It is a consequence of immunosuppression, with those most immunosuppressed being at greatest risk [1]. Prior to routine prophylaxis, the incidence was 5–15% in the first 6 months following solid organ transplant [1,2]. PCP causes significant morbidity and has a mortality rate of 30–60% in the non-HIV population [2–4]. Current guidelines recommend all renal transplant recipients receive prophylaxis, but there is no consensus on the optimum duration. The UK Renal Association suggests that trimethoprim-sulfamethoxazole (TMP-SMX) should be used as first-line prophylaxis for 3–6 months following renal transplant [5]. The European Renal Association suggests 4 months of prophylaxis and the American Transplant Association suggests 6 to 12 months [1,6]. Many centers recommend additional prophylaxis at times of increased immunosuppression, such as treatment of acute rejection [6]. TMP-SMX reduces the incidence of PCP by 85% and is recognized to have activity against common bacterial infections, including urinary pathogens [4]. It can also reduce the frequency of urinary tract infections (UTIs) [7,8].

Prior to 2015, our unit prescribed 3 months of TMP-SMX 480 mg daily as prophylaxis. However, following an outbreak of PCP in 2015, the duration was increased to 6 months, with an additional 6-month prophylaxis following any treatment for acute rejection [9]. TMP-SMX has several important potential adverse effects which can lead to cessation of treatment. Specifically, these include cytopenias (leucopenia and thrombocytopenia), increased serum creatinine, and increased serum potassium [4,6]. Theoretically, resulting cytopenias may result in reduction of immunosuppressant dosing. The benefits of increased duration of prophylaxis must therefore be carefully balanced against these risks.

We performed a retrospective observational cohort study to assess the impact of increased duration of TMP-SMX prophylaxis on frequency of UTI (including multi-resistant organisms), PCP cases, and adverse events (including cytopenias, transplant function assessed by estimated glomerular filtration rate [eGFR], serum potassium, and mycophenolate mofetil dosing).

Material and Methods

All renal transplant recipients with transplants performed between January 2012 and May 2016 were included in analysis, with at least 6 months of follow-up data for each patient.

A search of the Strathclyde Electronic Renal Patient Record (SERPR) was performed and data were extracted for eligible patients. This included baseline characteristics (age, primary renal diagnosis, previous renal replacement therapy, type of transplant); TMP-SMX prescription dates and dose; mycophenolate mofetil prescription dates and dose; and relevant laboratory measurements closest to post-transplant days 7, 90, 180, 270, and 365 (total white cell count, lymphocyte count, neutrophil count, serum potassium, and serum creatinine). We accepted a range of 7 days on either side of the intended day (except for day 7) after transplant. We also identified the lowest total white cell count and neutrophil count in the first 6 months. We obtained all urine culture results for the first 6 months after transplant.

In our unit patients receive standard transplant immunosuppression based on the ELITE-Symphony study [10]. All patients receive humanised monoclonal anti-IL2 receptor antibody induction, corticosteroid (a 500 mg intravenous bolus of methylprednisolone at the time of transplant, then 20 mg prednisolone daily, tapering to 5 mg daily by 6 months), mycophenolate mofetil (MMF) (1000 mg twice daily), and tacrolimus (0.05 mg/kg Prograf twice daily adjusted to achieve 12-h blood tacrolimus levels of 5–7 μg/L). Valganciclovir is given for 6 months as cytomegalovirus prophylaxis if the recipient is seronegative and the donor is seropositive. Urine is routinely sent for culture at every clinic visit for the first year after transplant.

Patients were divided into 2 cohorts according to the date of renal transplant, reflecting the change in prophylaxis duration from February 2015, and results were analyzed on an intention-to-treat basis. Secondary analysis was performed according to the actual duration of TMP-SMX prescribed to confirm that any differences in groups were a true reflection of differences in prophylaxis duration. To allow this, we recorded the start/stop dates of the first 2 prescriptions of TMP-SMX, and the total duration prescribed was calculated. We recorded 2 prescription dates in case of early discontinuation or suspension/re-prescription, to ensure we recorded the correct duration for each patient. For secondary analysis, patients receiving 80–100 days of TMP-SMX were included in the 3-month treatment group, and those receiving 160–200 days were included in the 6-month treatment group. All others were excluded.

Microbiological culture results were analyzed. Positive samples were recorded, and it was noted if the organism was multi-resistant. Clinical information on symptoms relating to each result was not available; therefore, UTI was defined as a single positive culture with >100 000 colony-forming units per milliliter (CFU/ml). Positive cultures with <100 000 CFU/ml were recorded as non-significant growth. Only cultures within 6 months of transplant were included. Persistent growth was defined as repeated culture of the same organism within 14 days of the previous sample. The European definition of multi-resistant organism was used, but we also included

Table 1. Baseline characteristics of patients.

		3 months (n=403)		6 months (n=177)		p Value
Age, mean (SD)		49.2	(12.7)	50.5	(13.2)	0.3
Sex	Female n (%)	159	(39.5)	78	(44.1)	0.41
	Male n (%)	244	(60.5)	99	(55.9)	0.52
Duration RRT* days pre-transplant, median (IQR)		958 (263–1978)		679 (150–1677)		0.92
Primary renal diagnosis	Glomerulonephritis n (%)	99	(24.6)	46	(25.9)	0.71
	Interstitial Nephropathies n (%)	147	(36.4)	71	(40.1)	0.41
	Diabetes n (%)	35	(8.7)	21	(11.9)	0.23
	Multisystem Disease n (%)	47	(11.7)	18	(10.2)	0.60
	Unknown or Other n (%)	75	(18.6)	21	(11.9)	0.46
Previous transplant (%)		63	(15.6)	28	(15.8)	0.95
Type of transplant	Live n (%)	116	(28.8)	48	(27.1)	0.68
	Deceased n (%)	287	(71.2)	129	(72.9)	
Donor age, mean (SD)		60	(13)	52	(28)	0.59

* RRT – renal replacement therapy.

vancomycin-resistant enterococci, as this is a particular problem in our patient population [11]. The frequency of UTI for each patient was calculated, with persistent growths excluded. All analyses were censored at the point of transplant failure.

Cases of PCP were identified by diagnostic coding in SERPR and a secondary review of all deaths in the cohort.

Statistical analysis was performed using Microsoft Excel 2015, version 15.13.1 (150807), Microsoft. Statistical differences in continuous variables were determined using a two-tailed *t* test; chi-squared tests were used for categorical variables. A p value of <0.05 was considered significant. The incidence rate of UTI was calculated for each patient group and the rate ratio was used to compare groups. Ethics approval was not required.

Results

There were 609 renal transplants carried out between 1 January 2012 and 31 May 2016. There were 418 patients prescribed TMP-SMX for 3 months (3-m). Fifteen were excluded due to transplant failure within 6 months (renal vein thrombosis [n=4], renal artery thrombosis [n=2], severe rejection [n=4], early bleeding [n=1], recurrence of previously unknown primary hyperoxaluria [n=1], and deaths due to stroke [n=1], pneumonia [n=1], and hyperkalemia [n=1]). None of these graft losses were due to UTI, PCP, or severe rejection as a result of immunosuppression reduction. The mean TMP-SMX prescription was 109.6 days (range, 1–3054 days). Four patients were

prescribed TMP-SMX for over 400 days: 2 were on long-term treatment due to granulomatosis with polyangiitis, 1 was on lifelong treatment due to a lung transplant, and 1 had HIV infection and previous PCP and thus was receiving prolonged prophylaxis. There were 191 patients prescribed TMP-SMX for 6 months (6-m). Fourteen were excluded due to transplant failure within 6 months (renal artery thrombosis [n=4], renal vein thrombosis [n=2], severe bleeding [n=2], thrombotic microangiopathy [n=1], transplant pyelonephritis [n=1], severe rejection [n=1], transplant renal artery stenosis [n=1], primary non-function [n=1], and 1 death due to sepsis at post-transplant day 12). None of these graft losses were due to UTI, PCP, or severe rejection as a result of immunosuppression reduction. The mean TMP-SMX prescription was 159.4 days (range, 1–344 days). Baseline characteristics for each cohort of patients were similar (Table 1).

For secondary analysis, patients were grouped according to the actual duration of TMP-SMX they received. There were 351 patients who received 80–100 days of treatment (actual treatment 3 months [AT 3-m]) with a mean duration of 96 days, and 159 patients who received 160–200 days. Seventy patients were excluded because they received TMP-SMX for a different duration. Baseline characteristics were again similar between groups.

Urinary tract infections

On intention-to-treat analysis, there was a significant difference between groups in patients experiencing at least 1 UTI (the 3-m

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Table 2. Incidence rate of urinary tract infection in 3-month *vs.* 6-month groups by intention to treat.

	3 m (n=403)	6 m (n=177)
Total no. UTI*	376	106
Patient days (n×180 days)	72,540	31,860
Incidence rate (per 100 patient days)	0.52	0.33
Multi-resistant organisms	28	0

The rate ratio is 1.57 (95% CI 1.27–1.95). * UTI – urinary tract infection.

group had 376 UTI in 133 patients [33%], while the 6-m group had 106 UTI in 42 patients [23%]; p=0.02). When culture results were analyzed according to time after transplant, there was a significant difference in the frequency of UTI occurring between groups at 0–3 months after transplant, when all patients were taking TMP-SMX (p=0.03). However, this difference was not present at 4–6 months after transplant when only patients in the 6-m group were taking TMP-SMX (p=0.13). On secondary analysis, there was no difference between groups (p=0.07).

The incidence rate of UTI was 0.52 UTI per 100 patient days in the 3-m group, and 0.33 UTI per 100 patient days in the 6-m group (Table 2). This gives a rate ratio of 1.58 (95% confidence interval 1.27–1.95) and suggests a lower incidence of

UTI in the 6-m group. However, the rate ratio was significantly elevated again when comparing groups at 0–3 m after transplant (1.78; 95% CI 1.34–2.37), but not by 4–6 months after transplant (1.31; 95% CI 0.94–1.82).

There was a significant difference in multi-resistant organisms between groups. There were 28 multi-resistant UTIs in 16 patients in the 3-m group, but there were no multi-resistant UTIs in the 6-m group (p=0.004). Twenty-one were extended-spectrum beta lactamase (ESBL) producers and 7 were vancomycin-resistant enterococci (VRE). This difference persisted on secondary analysis of actual treatment (the AT 3-m group had 21 multi-resistant organisms, while the AT 6-m group had 1 multi-resistant organism; p=0.02). There was no significant difference in the overall spectrum of organisms cultured.

Renal function

There was no significant difference in renal function between treatment groups when comparing estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease Study equation [12]. This was also the case on secondary analysis of actual treatment duration.

Serum potassium

There was no significant difference in serum potassium concentration between groups beyond day 6 after transplant (Table 3).

Table 3. Comparison of results from 3-month *vs.* 6-month intention-to-treat groups.

	Day 6	Day 89	Day 179	Day 269	Day 365
3 m mean eGFR* (mL/min/1.73 m²) (SD)	34.9 (29.5)	52.0 (21.0)	53.0 (21.0)	52.8 (21.5)	52.1 (21.4)
6 m mean eGFR* (mL/min/1.73 m²) (SD)	34.6 (28.4)	49.1 (20.8)	50.6 (20.0)	50.9 (19.4)	51.4 (19.9)
3 m mean serum potassium (mmol/L) (SD)	4.3 (0.6)	4.5 (0.5)	4.5 (0.5)	4.5 (0.5)	4.5 (0.5)
6 m mean serum potassium (mmol/L) (SD)	4.5 (0.6)	4.5 (0.5)	4.5 (0.5)	4.4 (0.5)	4.4 (0.5)
3 m mean total white cell count×10⁹/L (SD)	8.72 (3.67)	7.26 (3.35)	7.66 (2.94)	8.02 (2.76)	8.14 (2.69)
6 m mean total white cell count×10⁹/L (SD)	8.79 (3.50)	7.17 (3.09)	7.28 (3.21)	7.91 (2.76)	7.95 (2.31)
3 m mean neutrophil cell count×10⁹/L (SD)	6.41 (3.13)	5.28 (3.10)	5.60 (2.70)	5.84 (2.58)	5.88 (2.58)
6 m mean neutrophil cell count×10⁹/L (SD)	6.45 (2.98)	5.21 (2.80)	5.30 (2.91)	5.71 (2.45)	5.78 (2.12)
3 m mean lymphocyte cell count×10⁹/L (SD)	1.44 (0.92)	1.25 (0.66)	1.28 (0.69)	1.37 (0.69)	1.44 (0.73)
6 m mean lymphocyte cell count×10⁹/L (SD)	1.45 (0.93)	1.22 (0.63)	1.22 (0.62)	1.36 (0.71)	1.36 (0.64)
3 m mean platelet cell count×10⁹/L (SD)	211 (75)	250 (79)	346 (78)	239 (72)	242 (71)
6 m mean platelet cell count×10⁹/L (SD)	212 (76)	262 (74)	251 (76)	247 (72)	248 (72)
3 m mean MMF** total daily dose (g) (SD)	1.9 (0.4)	1.6 (0.5)	1.5 (0.5)	1.4 (0.5)	1.4 (0.5)
6 m mean MMF** total daily dose (g) (SD)	1.9 (0.4)	1.6 (0.5)	1.5 (0.6)	1.4 (0.6)	1.4 (0.6)

No statistically significant differences. * eGFR – estimated glomerular filtration rate; ** MMF – mycophenolate mofetil.

Cell counts

There were no significant differences in total white cell count, neutrophil count, or lymphocyte count between groups. However, on secondary analysis of actual treatment duration, there was a significant difference in lymphocyte count at day 179 after transplant, with a slightly lower lymphocyte count in those patients still being prescribed TMP-SMX (AT 3-m lymphocyte count 1.30×10^5/L; AT 6-m 1.15×10^5/L; p=0.02). The lowest absolute total white cell count and neutrophil count was identified for all patients. There were no significant differences in the proportion of patients in each group with lowest total white cell count in the first 6 months after transplant <3.5 or <1.0×10^9/L, or lowest neutrophil count in the first 6 months after transplant <1.0 or <0.5×10^9/L. There was no significant difference in total platelet count between groups (Table 3).

Mycophenolate mofetil dosing

There was no significant difference in the average total daily dose of mycophenolate mofetil between patient groups (Table 3).

Co-trimoxazole cessation

Thirty-seven patients discontinued co-trimoxazole before completing the intended period of prophylaxis. Reasons included allergy/intolerance (11 patients), lymphopenia (3 patients), hyperkalemia (2 patients), and abnormal liver function (2 patients). In 19 cases, the reason was unknown.

Pneumocystis pneumonia

At the time of data extraction, there had been 18 cases in our study population, with 7 deaths attributed. This gives an overall frequency of PCP of 3.1% and a mortality rate of 39%. The majority of cases were in the 3-month TMP-SMX prophylaxis cohort (ITT 3-m 15 cases, incidence 3.7%; ITT 6-m 3 cases, incidence 1.7%). All cases of PCP were at least 172 days after transplant: no patients were taking prophylaxis at the time. The mean time to diagnosis was 383 days after transplant, with 6 cases occurring beyond 1 year after transplant. All deaths were in the 3-month prophylaxis cohort.

Discussion

Our study confirms that UTI is common following renal transplant. In our cohort, the frequency of UTI does not seem to be reduced in patients taking TMP-SMX, in contrast to previous studies [7,8]. These studies included asymptomatic bacteriuria in their definition of UTI. While it initially seems there is a significant difference between rates of UTI, with more occurring in the 3-month treatment cohort, when this is studied more closely this difference between groups is present 0–3 months after transplant (when all are taking TMP-SMX) and not at 4–6 months. Similarly, the rate ratio of UTI also appears lower in the 6-month prophylaxis group, but this difference was also only present at 0–3 months after transplant. This apparent reduction in frequency of UTI cannot be attributed to TMP-SMX. It is unclear why this difference was present, with no obvious patient or laboratory reporting differences to explain it.

Emerging multi-drug-resistant organisms are a serious concern. We found 2.8% of patients in our cohort had at least 1 multi-drug-resistant UTI. All multi-drug-resistant UTIs occurred in the 3-m prophylaxis group. Specific trimethoprim resistance would be of interest; unfortunately, we could not analyze this due to the way the source microbiology laboratories report results. Other factors can influence the appearance of multi-resistant organisms. There has been increased focus on antimicrobial stewardship over the last few years, and, coupled with uncertainty about how to manage asymptomatic bacteriuria in the renal transplant population, it is possible that overall antibiotic usage may have declined during this time. The spectrum of antibiotics used may also have changed. Overall, this may have contributed to a reduction in the development of multi-resistant organisms in our population. Importantly, we have no evidence that extended TMP-SMX prophylaxis promotes the development of multi-resistant organisms. This is reassuring and reduces concern surrounding longer durations of TMP-SMX for PCP prophylaxis.

We have shown that TMP-SMX is safe to use in the renal transplant population, with no significant adverse impact on routine measures of renal function or serum potassium. The statistically significant difference in lymphocyte count on secondary analysis is very unlikely to be clinically significant given the difference in cell counts was so small. Theoretically, leukopenia could result in reduced dose of anti-proliferative agents and contribute to increased rejection risk. A recent study found 27% of kidney transplant recipients on prophylactic TMP-SMX developed cytopenias, all in the context of concurrent MMF and/or valganciclovir [13]. We are reassured that in our study there were no differences in dosages of anti-proliferative medication between prophylaxis groups. Our results are reassuring in that the contribution of TMP-SMX duration to leukopenia is minimal.

PCP has significant morbidity and mortality, and there is no consensus on the optimum duration of prophylaxis. Our study confirms the efficacy of TMP-SMX prophylaxis, with no patients developing PCP when taking it. The frequency (3.1%) and mortality rate (39%) of PCP in our cohort are similar to other published rates in the prophylaxis era [4]. The Glasgow outbreak is captured in the 3-month prophylaxis cohort with an incidence

of 3.7% compared to 1.7% in the 6-month cohort. It is tempting to interpret this reduction as a direct effect of extended prophylaxis; however, given the recognized outbreak, it is potentially explained by regression to the mean. It could be argued that the extended prophylaxis cohort had shorter follow-up and may still develop PCP. We therefore performed a database search for additional cases up to December 2017 and confirmed there were no new cases of PCP in the extended prophylaxis group.

Conclusions

Although PCP risk is highest in the first 6 months after renal transplant, it is not uncommon for patients to develop PCP many months later – 6 of our 18 cases of PCP occurred beyond

1 year after transplant, and the mean time from transplant to diagnosis was 383 days. This is consistent with other studies from the prophylaxis era, which found PCP often occurs many months after transplant [2,14]. Given the high associated morbidity and mortality, it could be argued that we should continue prophylaxis for 1 year, or perhaps even longer, as is already suggested by the American Society for Transplantation [1]. However, it should be noted that at least 3% of our study patients who were prescribed TMP-SMX ceased treatment because it was not tolerated. The alternative agents, including dapsone, have their own potentially serious adverse effects [15]. Overall, our study provides important safety data to reassure patients and prescribers considering extension of the TMP-SMX prophylaxis period after renal transplantation. Further studies are warranted to determine the optimum duration of prophylaxis for renal transplant recipients.

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