Switch to atovaquone and subsequent re-challenge with trimethoprim-sulfamethoxazole for \textit{Pneumocystis} prophylaxis in a kidney transplant population

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\textbf{Abstract}
Kidney transplant recipients who are switched to atovaquone (ATO) from trimethoprim-sulfamethoxazole (TMP/SMX) for \textit{Pneumocystis jirovecii} pneumonia (PJP) prophylaxis because of adverse events or complications may miss opportunities to be re-challenged with TMP/SMX, the first-line agent. This single-site, retrospective study assessed kidney transplant recipients for documented reasons for switching from TMP/SMX to alternate PJP prophylaxis and outcomes of TMP/SMX re-challenge. Out of 166 patients, 155 initially received TMP/SMX; of these, 31 were switched to ATO for various reasons. Fourteen patients receiving ATO were re-challenged with TMP/SMX; all were successfully re-initiated on TMP/SMX therapy. Most patients switched to ATO post kidney transplant secondary to non-hypersensitivity reasons should be re-challenged with TMP/SMX because of the advantages it provides over other agents.

\textbf{KEYWORDS}
atoquaone, kidney transplant, \textit{Pneumocystis jirovecii} pneumonia (PJP), prophylaxis, trimethoprim-sulfamethoxazole

\section{INTRODUCTION}

\textit{Pneumocystis jirovecii} pneumonia (PJP) is an important cause of morbidity and mortality in solid organ transplant recipients.\textsuperscript{1} In the absence of prophylaxis, the incidence of PJP after solid organ transplantation ranges from 5\% to 15\%, with the highest risk after lung transplantation and lowest risk after kidney transplantation.\textsuperscript{2} The risk of developing PJP is greatest within the first 6 months post transplant and is directly related to the intensity of immunosuppression.\textsuperscript{3} Because of this time-sensitive risk, anti-\textit{Pneumocystis} prophylaxis administered for at least 6 months post transplant is recommended for solid organ transplant recipients and this strategy is associated with marked reduction in incidence of PJP.\textsuperscript{1,3,4} According to the current practice recommendations, trimethoprim-sulfamethoxazole (TMP/SMX) is the preferred agent for PJP prophylaxis.\textsuperscript{5} Unfortunately, approximately 9\%-40\% of transplant recipients do not tolerate TMP/SMX because of adverse reactions or allergy and require alternative prophylaxis.\textsuperscript{6,7} Adverse effects of TMP/SMX include, but are not limited to, bone marrow suppression, rash, acute kidney injury, and hyperkalemia. Patients are commonly switched to atovaquone (ATO) or dapsone, which are considered second-line agents, when these adverse reactions are identified.\textsuperscript{5} In the case of ATO, this agent costs substantially more than TMP/SMX.\textsuperscript{8}

As many TMP/SMX-associated adverse reactions are transient, clinicians should consider reinstituting this first-line agent after the adverse reaction resolves. However, many patients are not re-challenged with TMP/SMX and therefore remain on second-line therapy. These patients may be subjected to an increased incidence of other infections as well as higher drug cost.\textsuperscript{9,10} A previous study in human immunodeficiency virus (HIV)-infected patients has
shown that it is possible to successfully reintroduce TMP/SMX to patients who experienced mild-to-moderate adverse reactions. The objective of this study was to assess the reasons for patients being switched from TMP/SMX to ATO for PJP prophylaxis following kidney transplantation and to determine if these patients had been successfully re-challenged with TMP/SMX.

2 | PATIENTS AND METHODS

This retrospective, cohort study was conducted at Northwestern Memorial Hospital (NMH), an urban tertiary university hospital with a robust solid organ transplant program, located in Chicago, IL, USA. Kidney transplant recipients 18 years or older and receiving prophylaxis for PJP from July 1, 2012 through December 31, 2012 were considered for inclusion. Per transplant center protocol, organ recipients receive daily oral TMP/SMX (80 mg/400 mg) beginning immediately post transplant unless contraindicated. Patients with TMP/SMX allergy or intolerance receive oral ATO 1500 mg daily. Patient allergy information, information regarding PJP prophylaxis, neutropenia, potassium levels, and TMP/SMX re-challenge information were collected. Patients were re-challenged at the discretion of their attending physician. Currently, no protocol is in place for re-challenge with TMP/SMX. Patients were assessed for the documented reason(s) and timing of the switch from TMP/SMX to ATO or other PJP prophylaxis. This study was reviewed and approved by the Institutional Review Boards at Northwestern University and Midwestern University. Descriptive statistics were compiled and all analyses were performed using Microsoft Excel®.

3 | RESULTS

During the study period, 166 kidney recipients met criteria for study inclusion (Figure 1). Of these, 155 patients (93.4%) received initial prophylaxis with TMP/SMX and 11 patients (6.6%) received ATO. Those with adverse reactions to TMP/SMX (n = 31, 20%) were switched to ATO a median 78 days (interquartile range [IQR] 36-115 days; range 3-323 days) after transplant. The reasons for switching included neutropenia (n = 20, 64.5%), allergic reaction (n = 3, 9.7%), hyperkalemia (n = 1, 3.2%), pruritus (n = 2), acute kidney injury (n = 1), liver injury (n = 1), and unknown (n = 3, 9.7%).

Fourteen patients (45.2%) were re-challenged with TMP/SMX and all 14 of these patients (100%) were successfully re-started on TMP/SMX. The median time to reintroduction was 155 days (IQR 74-318) after switching from ATO (range 4-450 days; Figure 2). Seventeen patients (54.8%) remained on ATO and were not re-challenged. These patients were switched from TMP/SMX because of neutropenia (52.9%), allergy/pruritus (23.5%), and unknown/other reasons (23.5%).

4 | DISCUSSION

At our center, most kidney transplant recipients who were switched to ATO because of non-hypersensitivity reactions, neutropenia, and other transient adverse effects were not re-challenged with TMP/SMX. All patients who were re-challenged with TMP/SMX tolerated its re-institution. Despite this high likelihood of successful reintroduction of TMP/SMX prophylaxis, clearly opportunities are missed for TMP/SMX re-challenge.

![Figure 1](https://example.com/figure1.png)

**Figure 1**: Reasons for initiation and switches in prophylaxis. TMP/SMX, trimethoprim-sulfamethoxazole; ATO, atovaquone; ANC, absolute neutrophil count; IQR, interquartile range; K+, potassium

*Potential for cholestatic liver injury (n=1), renal insufficiency (n=1), itching (n=2)
Improved documentation of reasons for switching to ATO may allow for a better understanding of situations for potential re-challenge and may help to reduce the use of ATO when TMP/SMX is an option, as has been shown in a previous retrospective study assessing HIV-infected patients receiving ATO and the clinical appropriateness of the choice of and continued indication for PJP prophylaxis. Other studies have shown the successful reinstatement of TMP/SMX for PJP prophylaxis after resolution of a transient mild-to-moderate adverse reaction. A study conducted by Leoung et al indicates that successful re-introduction of TMP/SMX in HIV patients who previously experienced adverse effects is relatively safe, either through dose-escalation or direct re-challenge. Patients’ success was determined by their ability to receive one single-strength TMP/SMX dose daily for 6 months. Patients with previous rash or fever were successfully able to restart on TMP/SMX with a dose-escalation over a 6-day time-period. Patients who were not exposed to the drug for 8 weeks were also able to successfully restart the medication using a simple, direct re-challenge. A study of orthotopic liver transplant patients saw bone marrow suppression in 14 of 28 patients; however, this adverse effect did not worsen in those patients who continued TMP/SMX.

Care should be taken when initiating and re-initiating TMP/SMX in this patient population. Mitsides et al found a high rate of complications among kidney transplant recipients receiving TMP/SMX for prophylaxis during a PJP outbreak; the most common complication was an increase in serum creatinine. The only significant factors linked to acute kidney injury by multivariable analysis were elevated baseline estimated glomerular filtration rate and an increased age of transplant in years. Only five patients (2%) developed leukopenia; the article does not clarify how many of these patients were enrolled during the first 6 months post transplant, as in our cohort. Of note, most of the enrolled patients had older renal transplants and several had received more than one kidney transplant. At our center, neutropenia was the most common event prompting a change in prophylactic agent; after neutrophil recovery, these patients tolerated TMP/SMX re-challenge (Figure 2).

Furthermore, 100% of re-challenges with TMP/SMX were successful, regardless of the initial adverse event that prompted discontinuation. The high frequency of neutropenia seen in our cohort may be attributed to the time frame of this study (ie, first 6 months early post transplant). Time-sensitive systematic alerts or flags for PJP prophylaxis may be beneficial in electronic medical records after this time frame, to assist with identifying patients for potential TMP/SMX re-challenge.

Limitations of this study include its retrospective and single-center design; however, we were able to assemble a cohort that included a variety of reasons for switching from TMP/SMX to ATO and identified potential missed opportunities to switch back to TMP/SMX.

5 | CONCLUSION

In the majority of cases, kidney transplant recipients who develop adverse reactions to TMP/SMX prophylaxis that prompt change to a second-line agent because of non-hypersensitivity reasons, may be re-challenged with TMP/SMX as appropriate because of the advantages TMP/SMX provides over other agents. We aim to further support the use of TMP/SMX as the primary agent for prophylaxis in kidney transplant patients and improve documentation regarding adverse reactions.

AUTHOR CONTRIBUTIONS

M.M.M., V.O.B., V.S., and S.S. designed the study and performed the statistical analyses. M.M.M., C.R., and A.G. acquired clinical data. M.M.M., C.R., P.M., and N.P. drafted and critically revised the report. All authors read and approved the final report.

CONFLICT OF INTEREST STATEMENT

All authors: no relevant conflicts.

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