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Trimethoprim/sulfamethoxazole for nocardiosis in solid organ transplant recipients: Real-life data from a multicentre retrospective study

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Abstract

Background: Little is known regarding the optimal management of nocardiosis among solid organ transplant (SOT) recipients. It is often suggested to avoid trimethoprim/sulfamethoxazole (TMP-SMX) monotherapy in heavily immunocompromised patients (such as SOT recipients) and/or in case of severe or disseminated nocardiosis. Our aim was to report our experience with TMP-SMX monotherapy in SOT recipients with nocardiosis.

Abbreviations: 16S rRNA, 16S ribosomal RNA; AE, adverse events; AKI, acute kidney injury; ALT, Alanine aminotransferase; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; EPO, erythropoiesis-stimulating agent; ISCL, increases in serum creatinine level; SCr, serum creatinine; SOT, solid organ transplant; TMP-SMX, trimethoprim/sulfamethoxazole.

Methods: Using data from a previously published European study, we assessed the incidence of adverse events in SOT recipients receiving TMP-SMX monotherapy and assessed its effectiveness.

Results: Thirty-one SOT recipients with nocardiosis were included, mostly kidney transplant recipients (20/31, 65%). Eleven (36%) had disseminated infection, and four (13%) had brain nocardiosis. Most patients had lung and/or pleural involvement (26/31, 84%). Daily dose of trimethoprim at initiation was 10 [6.4-14.8] mg/kg. The median estimated glomerular filtration rate at time of diagnosis of nocardiosis was 44 [30-62] ml/min/1.73 m^2. TMP-SMX was discontinued prematurely in one third of the patients (10/31, 32%, mostly for hematological toxicity [n = 3] or increased serum creatinine [n = 3]). Focusing on the 24 (77%) patients who completed at least 30 days of TMP-SMX monotherapy, 4 had late (>30 days) drug discontinuation, 1 experienced treatment failure, and 19 completed planned TMP-SMX monotherapy. Clinical outcome was favorable in these 19 patients, despite the fact that 8 (42%) had disseminated infection and 2 (11%) brain nocardiosis. Overall, all-cause 1-year mortality was 10% (3/31).

Conclusions: TMP-SMX monotherapy appears to be effective for the treatment of most nocardiosis among SOT recipients. Interventional studies are needed to compare its safety and effectiveness with those of other regimens used to treat post-transplant nocardiosis.

KEYWORDS

acute kidney injury, cotrimoxazole, transplantation, trimethoprim/sulfamethoxazole

1 | INTRODUCTION

Nocardiosis is a rare opportunistic infection, affecting 0.04%-3.5% of patients after solid organ transplantation (SOT).[1-4] Despite the fact that SOT recipients with nocardiosis have a 1-year mortality rate between 10% and 20%,[2] little is known about the optimal management of nocardiosis in this setting. Although several antimicrobial agents may be useful in the treatment of nocardiosis (eg, trimethoprim/sulfamethoxazole, carbapenems, third-generation cephalosporins, aminoglycosides, and linezolid), real-life data on the benefits and harms of these drugs in SOT recipients with nocardiosis are lacking. Results from in vivo experiments have suggested that combinations of bactericidal antibiotics (such as imipenem and amikacin) may be associated with better outcomes and are often recommended in SOT recipients with nocardiosis.[5] In contrast, trimethoprim/sulfamethoxazole (TMP-SMX) is not bactericidal against *Nocardia* but has, however, multiple advantages: it has excellent in vitro activity against almost all *Nocardia* spp., diffuses to all body sites, may be administered orally, and is cheap.[6] Regrettably, little is known about its effectiveness and safety in SOT recipients with nocardiosis. Regarding safety, a retrospective study including 214 patients receiving short-course (median duration, 7 days) TMP-SMX, mostly for respiratory or skin and soft tissue infections, identified that 42 patients (19.6%) met acute kidney injury criteria and 33 (15.4%) experienced hyperkalemia.[7] However, SOT recipients with nocardiosis receive TMP-SMX at higher dose (10-20 mg of TMP/kg/d) and longer duration (~6 months). Data in this specific context are therefore required.

We recently performed a multicenter retrospective study on nocardiosis in European SOT patients.[2,8] Using data from that study, we describe our clinical experience in SOT recipients who received TMP-SMX monotherapy for *Nocardia* infection.

2 | METHODS

2.1 | Ethics

The original study[8] was approved by local ethics committees and fulfilled the regulatory standards of each participating country. The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

2.2 | Study participants

We analyzed data from a previously published multicenter retrospective European study,[8] in which patients with nocardiosis were

included if they met the following criteria: (1) SOT recipient; (2) *Nocardia* spp. isolated by culture of a clinical sample after transplantation; (3) presence of signs and/or symptoms suggestive of nocardiosis; and (4) diagnosis made between January 2000 and December 2014. For the present analysis, we included patients who received TMP-SMX monotherapy (defined as those who received TMP-SMX alone, or combined with another antibiotic for <5 days, within the first 15 days after diagnosis of nocardiosis). Even if TMP/SMX is a combination of two antibiotics (trimethoprim and sulfamethoxazole), the word "monotherapy" is used throughout the manuscript for simplicity.

2.3 | Objectives

First, we assessed the tolerance of TMP-SMX monotherapy among included patients and determined the number of patients who discontinued TMP-SMX prematurely. Second, we assessed the clinical effectiveness of TMP-SMX monotherapy (measured by cure rate and risk of relapse), with a particular focus on patients who received a significant course of TMP-SMX (defined as those who received more than 30 days of TMP-SMX monotherapy).

2.4 | Clinical data and definitions

In addition to previously collected data,[8] we sent a form to local investigators to collect supporting information for each eligible patient. This additional form included data recorded at TMP-SMX initiation (body weight, date of initiation of therapeutic TMP-SMX, and trimethoprim daily dose) as well as follow-up data at 1- and 2-month post-TMP-SMX initiation (leucocyte count, platelet count, ALT concentration, serum creatinine [SCr] concentration, estimated glomerular filtration rate [eGFR], and trimethoprim daily dose). We also collected data on potential TMP-SMX cessation (date and reason) and occurrence of adverse events (AEs, defined as any untoward medical occurrence[9]). We specifically focused on the following AEs: hyperkalemia (>5 mmol/L), thrombocytopaenia (<50,000 platelets/mm^3), anemia requiring transfusion, and/or erythropoiesis-stimulating agents, transaminitis (ALT value greater than normal), and neutropenia (<500/mm^3). Increases in SCr were characterized using the KDIGO classification for acute kidney injury (KDIGO-1 for increase ≥0.3 mg/dl or 1.5-1.9 times baseline, KDIGO-2 for increase 2-2.9 times baseline, and KDIGO-3 for increase ≥3 times baseline or initiation of renal replacement therapy.[10]) As some of these increases in SCr may be related to TMP-SMX-induced inhibition of tubular creatinine secretion, we do not refer to them as "acute kidney injury (AKI)".[22] Early and late discontinuations of TMP-SMX were separated according to the timing of TMP-SMX cessation (ie, within the first 30 days after initiation of TMP-SMX versus later). Myelosuppression was defined as a decrease in red blood cells (anemia requiring transfusion and/or erythropoiesis-stimulating agents) AND white blood cells (leucocyte count <4 × 1000/mm^3) AND platelets (<150 × 1000/mm^3). The date of diagnosis was defined as the day on which the first clinical sample that yielded *Nocardia* spp. was collected. Cure was defined as clinical and radiological improvement associated with the absence of relapse during follow-up. Among those who survived, follow-up lasted at least 1 year. Relapse was defined as new signs of infection associated with the identification of the same *Nocardia* species.[11]

2.5 | Microbiology

Briefly, identification of *Nocardia* species required the amplification and sequencing of a fragment of the gene coding for the 16S ribosomal RNA (16S rRNA) or *hsp65*, as previously described.[8] Ideally, antibiotic susceptibility testing was performed by determination of the MIC in broth dilution but MICs evaluated by E-test strips or antibiotic disk diffusion on agar plates were considered acceptable when performed by a trained microbiologist.[2,8,12]

2.6 | Statistical methods

A descriptive analysis was performed after all data had been collected and verified. Categorical variables are given as numbers and proportions. Continuous variables are summarized as medians with interquartile range. Data were compiled and analyzed using an EXCEL® spreadsheet (Microsoft, WA, USA) and XLSTAT® software version 19.4. We compared patients' baseline characteristics between cases with or without TMP-SMX discontinuation using Fisher exact tests for categorical variables and nonparametric Mann–Whitney tests for continuous variables.

3 | RESULTS

3.1 | Characteristics of included patients

Thirty-one patients met the inclusion criteria (Figure 1). Patient characteristics are summarized in Table 1. The median age of the 31 patients was 60 [46-67] years at diagnosis of nocardiosis, and 18 (58%) were male. The median eGFR at time of diagnosis of nocardiosis was 44 [30-62] ml/min/1.73 m². Among the 31 SOT recipients who received TMP-SMX monotherapy, the most frequently transplanted organ was the kidney (20/31, 65%).

Ten of the patients (32%) had an additional microbial pathogen identified at the time of diagnosis: bacterial pneumonia (n = 5), invasive aspergillosis (n = 4), invasive cytomegalovirus (CMV) disease (n = 2), *Clostridioides difficile*-associated colitis (n = 1), and *Pneumocystis jirovecii* pneumonia (n = 1).

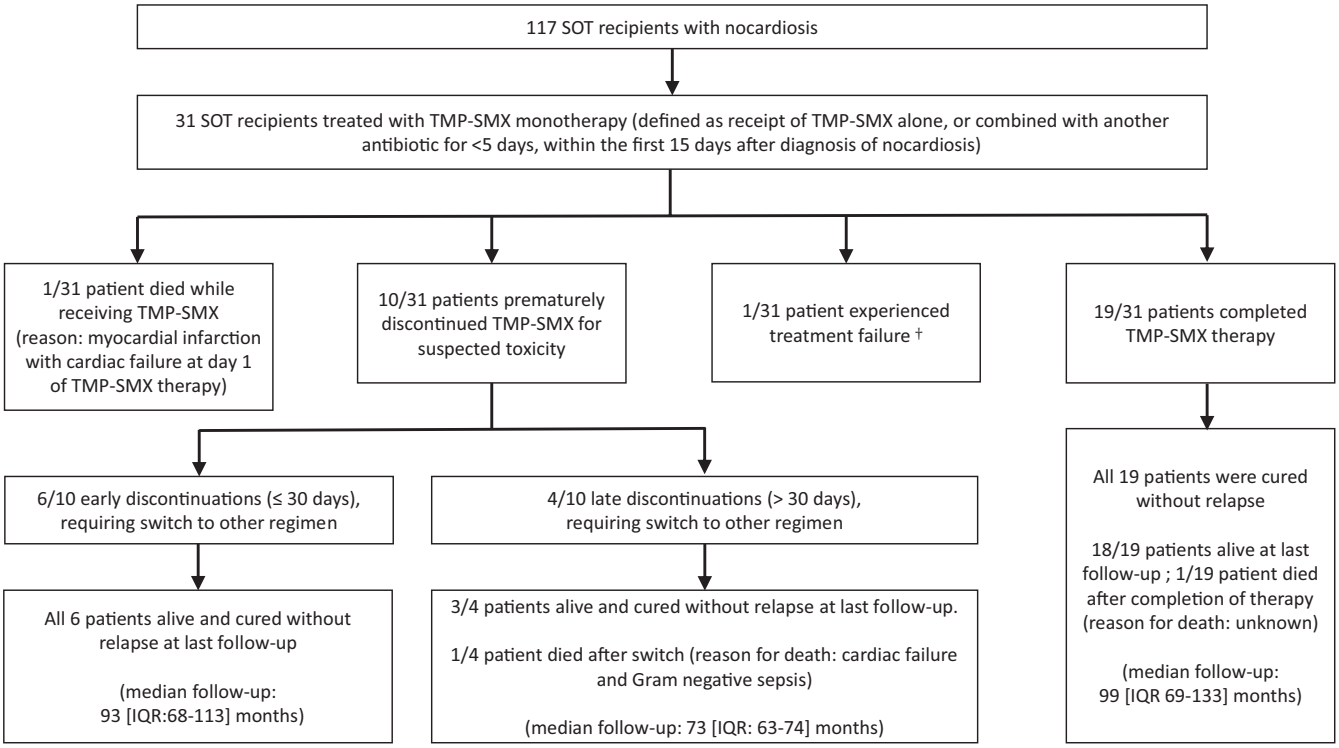

FIGURE 1 Flow-chart of 31 solid organ transplant recipients with nocardiosis treated with trimethoprim/sulfamethoxazole monotherapy. Note: TMP-SMX = Trimethoprim/sulfamethoxazole, SOT = solid organ transplant. † 39-year-old female kidney transplant recipient with lung nocardiosis and initial improvement after initiation of TMP-SMX. Three months later, the patient presented lung infiltrates on chest X-ray and a new bronchoalveolar lavage grew *Nocardia* spp., still susceptible in vitro to TMP-SMX. Nonadherence to TMP-SMX was suspected, and antimicrobial therapy was switched to imipenem and minocycline with success. This patient was alive and cured at last follow-up, 63 months after diagnosis of *Nocardia* infection.

3.2 | Tolerance of TMP-SMX monotherapy

Overall, TMP-SMX was discontinued in 10 of the 31 patients (32%) because of toxicity. In six patients (19%), TMP-SMX was discontinued in the first 30 days (one patient with anemia; one patient with transaminitis and KDIGO-2 increase in SCr; one patient with transaminitis; one patient with KDIGO-1 increase in SCr and hyperkalemia; one patient with myelosuppression; and one patient with increase in SCr with unknown KDIGO class and anemia). These six patients were subsequently treated with amoxicillin/clavulanate, carbapenemsm or amikacin. In four patients (13%), TMP-SMX was discontinued after day 30 (three patients with increase in SCr [2 KDIGO-1 and 1 KDIGO-2] and one patient with KDIGO-1 increase in SCr and neutropenia). No significant baseline characteristic differences were observed when we compared the 10/31 patients who experienced TMP-SMX discontinuation due to toxicity to the 19/31 who completed treatment as planned (supporting information **Table S1**).

To obtain additional information of the tolerance of TMP-SMX monotherapy, we contacted local investigators to retrieve supporting information for included patients. Additional clinical report forms were returned for 21/31 patients (response rate: 68%). A total of 31 AEs were reported in 19 of these 21 patients (90%). The most frequent AE associated with TMP-SMX use was increased Scr, which occurred in 12/21 (57%) patients (8 KDIGO-1, 2 KDIGO-2, 1 KDIGO-3, 1 patient without additional details). Six of the 12 patients who experienced increased SCr were kidney transplant recipients (50%). Hyperkalemia and anemia occurred in seven (33%) and six (29%) of the patients, respectively. One patient had both increased SCr and transaminitis, one patient had both increased SCr and hyperkalemia, one patient had both anemia needing transfusion, one patient had myelosuppression, and one patient had both diarrhea and transaminitis. Among six patients whose initial eGFR was <30 ml/min/1.73 m^2), four had increased SCr leading to TMP-SMX discontinuation in three cases (supporting information **Table S2**). Patients with low eGFR (≤60 ml/min/1.73 m^2) received similar daily doses of TMP-SMX to those with eGFR >60 ml/min/1.73 m^2).

Of the 10 patients without an additional clinical report forms, 9 completed the treatment as scheduled and only 1 had to discontinue TMP-SMX, because of myelosuppression.

3.3 | Effectiveness of TMP-SMX monotherapy

Among all 31 included patients, the 1-year all-cause mortality rate was 9.7% (3/31). Specifically, one patient died the day after starting TMP-SMX because of acute cardiac failure, another patient died after TMP-SMX was changed to another antibiotic because of

TABLE 1 Characteristics of 31 solid organ transplant recipients with nocardiosis treated with trimethoprim/sulfamethoxazole monotherapy

Characteristics	Full cohort (n = 31)	Patients who completed at least 30 days of TMP-SMX monotherapy (n = 24)
Clinical characteristics		
Age at diagnosis, years	60 [46-67]	57 [44-67]
Male	18 (58)	13 (54)
Transplanted organ, n (%)		
Kidney	20 (65)	15 (61)
Heart	5 (16)	5 (21)
Lung	3 (9)	1 (1)
Liver	2 (6)	2 (8)
Kidney and pancreas	1 (3)	1 (4)
Use of antiproliferative agents at diagnosis	22 (68)	16 (67)
Use of cyclosporine at diagnosis	9 (29)	8 (33)
Use of tacrolimus at diagnosis	5 (16)	3 (13)
TMP-SMX prophylaxis at diagnosis	5 (16)	3 (13)
Weekly dose of TMP prophylaxis (mg/kg)	0.71 [0.32-1.63]	1.21 [0.66-1.63]
Time from transplantation to diagnosis (days)	355 [123-720]	316 [119-773]
Diabetes mellitus	11 (35)	8 (33)
Acute rejection before *Nocardia*	15 (48)	11 (46)
Acute rejection in the year before *Nocardia* infection	11 (35)	8 (33)
Nocardiosis characteristics		
Time from symptoms to diagnosis, days	19 [8-30]	17 [7-30]
Involved organs		
Lung or pleural involvement	26 (84)	20 (83)
Skin and soft-tissue involvement	11 (36)	7 (29)
Central nervous system involvement	4 (13)	2 (8)
Bone or joint infection	1 (3)	1 (24)
Disseminated infection	11 (36)	8 (33)
Lung +skin and soft tissue	6	5
Lung +skin and soft tissue +central nervous system	2	0
Lung +central nervous system	2	2
Lung +central nervous system	1	2
Bone +skin and soft tissue	1	1
N *farcinica*	11 (4) {n = 26}	8 (38) {n = 21}
N *nova* complex	4 (15) {n = 26}	3 (14) {n = 21}
N *cyriacigeorgica*	3 (12) {n = 26}	3 (14) {n = 21}
Strain susceptible to TMP-SMX	28 (97) {n = 29}[a]	23 (96) {n = 24}[a]
Treatment of nocardiosis		
Daily dose of TMP at initiation (g)	0.48 [0.32-0.68] {n = 27}	0.48 [0.32-0.68] {n = 22}
Daily dose of TMP at initiation (mg/kg)	10 [6.4-14.8] {n = 19}	10.8 [6.8-13.8] {n = 14}
TMP-SMX duration (days)	146 [53-181] {n = 30}	180 [123-197] {n = 23}
Reason for stopping TMP-SMX		
End of treatment	19 (61)	19 (79)
Toxicity	10 (32)	4 (17)
Lack of adherence	1 (3)	1 (4)

(Continues)

TABLE 1 (Continued)

Characteristics	Full cohort (n = 31)	Patients who completed at least 30 days of TMP-SMX monotherapy (n = 24)
Death	1 (3)	0 (0)
Secondary prophylaxis	1 (3)	0 (0)
Biological findings		
Leucocyte count (x1000/mm^3)		
At time of diagnosis	11 [6-15] {n = 29}	11 [7-16] {n = 14}
Month 1	6 [5-8] {n = 18}	6 [5-8] {n = 14}
Month 2	4 [3-6] {n = 16}	4 [3-6] {n = 14}
Platelet count (x1000/mm^3)		
At time of diagnosis	247 [226-326] {n = 21}	248 [219-330] {n = 17}
Month 1	231 [181-310] {n = 17}	235 [207-301] {n = 15}
Month 2	254 [181-278] {n = 16}	254 [179-294] {n = 15}
Estimated glomerular filtration rate (ml/min/1.73 m^2)		
At time of diagnosis	44 [30-62] {n = 30}	44 [31-59] {n = 23}
Month 1	31 [21-47] {n = 17}	30 [22-41] {n = 14}
Month 2	41 [23-54] {n = 17}	41 [23-54] {n = 15}
Transaminitis		
At time of diagnosis	2 (10) {n = 21}	1 (4) {n = 16}
Month 1	2 (6) {n = 18}	0 (0) {n = 15}
Month 2	1 (7) {n = 15}	0 (0) {n = 13}
Adverse events		
Increased SCr	12 (57) {n = 21}	9 (60) {n = 15}
Hyperkalemia	7 (33) {n = 21}	6 (40) {n = 15}
Anemia requiring blood transfusion or EPO	6 (29) {n = 21}	4 (27) {n = 15}
Transaminitis	5 (16) {n = 21}	2 (13) {n = 15}
Neutropenia <500/mm^3	1 (3) {n = 21}	1 (17) {n = 15}
Platelet count <50 000/mm^3	0(0) {n = 21}	0 (0) {n = 15}
Outcome		
Alive 6 months after diagnosis	28 (90)	23 (96)
Alive 12 months after diagnosis	28 (90)	23 (96)
Relapse during follow-up	0 (0)	0 (0)

Note: Data are presented as No. (%) unless otherwise indicated for categorical variables and as median [interquartile range] for continuous variables. Full cohort: SOT patients receiving TMP-SMX monotherapy within 15 days of diagnosis AND less than 5 days of combination with other antibiotics. {n =} number of patients with available data (when <31 or 24).

Abbreviations: EPO, erythropoiesis-stimulating agent; SOT, solid organ transplant; TMP-SMX, trimethoprim/sulfamethoxazole.

[a]The only patient with a *Nocardia* isolate classified as resistant to TMP-SMX received a 180-day course of TMP-SMX and was considered as cured without relapse after more than 1 year of follow-up.

myelosuppression (died because of sepsis and cardiac failure), and a third patient died after having completed TMP-SMX therapy.

To evaluate the effectiveness of TMP-SMX monotherapy, we particularly focused on the 24 patients (80%) who received at least 30 days of TMP-SMX monotherapy (see Figure 1). As described earlier, TMP-SMX was subsequently discontinued (ie, after >30 days) in four patients because of AEs. In one additional case, TMP-SMX was stopped because of a relapse in the context of patient nonadherence (see details in Figure 1). Thus, 19 of these 24 (79%) patients completed treatment with TMP-SMX monotherapy (median duration 180 [156-230] days). All were cured and none relapsed during 99 [69-133] months of follow-up. Among these 24 patients, 15 had lung or pleural involvement, 8 had disseminated infection, and 2 had a brain abscess.

4 | DISCUSSION

In this retrospective study of 31 SOT recipients who received TMP-SMX monotherapy to treat nocardiosis, we identified a high

frequency of AEs (leading to premature discontinuation of TMP-SMX in one third of the patients) but observed that outcome was favorable in almost all the patients who tolerated the treatment.

A combination of bactericidal drugs (cephalosporins, imipenem, and/or amikacin) is often suggested for the treatment of disseminated or central nervous system nocardiosis or among immunocompromised patients.[5] Because of its bacteriostatic effects in animal models, many authors have suggested avoiding TMP-SMX monotherapy in patients with severe or disseminated nocardiosis.[13-16] This statement also stems from retrospective studies of immunocompromised patients that demonstrated a high mortality rate when TMP-SMX was used alone.[17,18] However, TMP-SMX monotherapy appears to be an attractive option because it has good oral availability and achieves high tissue concentrations, including in the central nervous system.[19,20] In addition, TMP-SMX is active against almost all *Nocardia* species [1,6,21]: a study of 552 clinical *Nocardia* isolates submitted to six laboratories demonstrated that only 0.5% of them were resistant to TMP-SMX.[6] Moreover, the low cost of TMP-SMX is an advantage when treatment duration is extended beyond 6 months. Finally, in a recent study assessing factors associated with 1-year mortality in nocardiosis after SOT, use of a multiple-drug regimen was not associated with improved survival.[2]

The main concern regarding the use of TMP-SMX remains tolerance, and more specifically, nephrotoxicity is a commonly feared AE of TMP-SMX. However, the reported prevalence of nephrotoxicity should be assessed cautiously because of the systematic increase in creatinine concentration that can occur when taking trimethoprim/sulfamethoxazole due to its inhibitory effects on tubular creatinine secretion, with no modification of the measured GFR.[22,23] This means that a moderate (ie, up to 20%–30%) increase in creatinine concentration, with no other AE should not prompt TMP-SMX interruption but rather encourage close monitoring and possibly the use of noncreatinine-based equations (eg, cystatin C) to assess renal function. In our study, 12 (57%) patients had an increase in SCr, leading to discontinuation in seven cases; increased SCr was the only reason for the discontinuation in three cases. However, most of the patients with increased SCr (8/12) were KDIGO-1, suggesting that in some of them, the increased SCr was likely related to decreased tubular creatinine secretion rather than to a decrease in the GFR. Although the frequency of AEs does not seem to have been related to the eGFR at the start of TMP-SMX, we observed that the discontinuation rate for AEs was higher when the eGFR was <30 ml/min/1.73 m² (notably discontinuation because of increased SCr). In our study, no dose adjustment was made in patients with eGFR <30 ml/min/1.73 m² even though several studies[7,24,25] strongly support this approach. This factor may also partly explain the high rate of discontinuation for increased SCr in our patients.[24,25]

Among patients who tolerated TMP-SMX monotherapy, clinical cure was achieved in 95% (19/20), without relapse during follow-up. In the remaining patient, TMP-SMX was stopped because of treatment failure in the context of patient nonadherence. Overall, all-cause 1-year mortality was 10% (3/31) which is in keeping with previous studies.[3,4]

Our study has several limitations including its retrospective design. Our study was not randomized, raising concerns about selection bias and imbalance of baseline characteristics between the 31 patients who received TMP-SMX monotherapy and the remaining 86 patients who received other regimen in our cohort of 117 SOT recipients with nocardiosis. We compared the main characteristics of the 31/117 patients included in the current study with those of the 86/117 remaining patients (see supporting information Table S3). Among the 31 SOT recipients who received TMP-SMX monotherapy, the most frequently transplanted organ was the kidney (20/31, 65%); this was similar to the remaining 86 patients included in our overall cohort of 117 SOT recipients with nocardiosis (20/31 [65%] versus 49/86 [57%], P =.46). The 31 patients who received TMP-SMX monotherapy were not significantly less likely to have a disseminated infection (11/31 [36%] versus 39/86 [45%], P = .34) or to have brain nocardiosis than the remaining 86 patients who received other antimicrobial regimen (4/31 [13%] versus 26/86 [30%], respectively, P = .14). However, our ability to detect differences between the two groups was limited by the relatively small numbers of patients. As a consequence, the validity of our results is uncertain in patients with brain nocardiosis and in patients whose transplanted organ is not kidney. We agree with the general recommendation that brain nocardiosis should be treated with intravenous and/or combination therapy. Another limitation was the absence of data on possible reduction or tapering of immunosuppressive drugs or compliance to therapy. Ten/31 patients had co-infections. While there is little doubt that these patients truly had Nocardia infection (given that all had lesions suggestive of nocardiosis on imaging with positive bronchoaspiration, bronchoalveolar lavage or blood culture for Nocardia), these additional infections and their management probably impacted the patient outcomes. Furthermore, only one patient from our cohort had a Nocardia isolate found to be in vitro resistant to TMP-SMX. The relatively high effectiveness of TMP-SMX observed in our study may of course not be applicable to settings where Nocardia resistance to TMP-SMX is more common. Lastly, the overall response rate for additional safety data was only 68%.

In conclusion, our results suggest that TMP-SMX monotherapy may be a suitable option for the treatment of nocardiosis in SOT patients, with a 95% cure rate, even in disseminated disease, when well tolerated. AEs remain the main limitation to its use and can lead to discontinuation of treatment in up to 30% of patients. However, the reported frequency of renal dysfunction may be overestimated because TMP-SMX can inhibit creatinine secretion resulting in increased serum creatinine concentrations; this possibility should be considered before TMP-SMX discontinuation. Interventional studies are needed to compare the safety and effectiveness of TMP-SMX monotherapy with those of other regimens used to treat posttransplant nocardiosis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

P. L. Conan, J. Coussement, and D. Lebeaux participated in research design, data analysis, and wrote the manuscript. M. Matignon, A. Bleibtreu, H. Guillot, S. Van Laecke, H. Brenier, R. Crochette, G. Melica, M. Fernández-Ruiz, J. Dantal, L. N. Waiti, C. Levi, C. Chauvet, J. De Greef, S. D. Marbus, N. J. Mueller, M. Ieven, F. Vuotto, and O. Lortholary contributed to the patients''care, reviewed, and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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