Combination of Echinocandins and Trimethoprim/Sulfamethoxazole for the Treatment of *Pneumocystis jiroveci* Pneumonia After Heart Transplantation

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ABSTRACT

Background. The echinocandins have shown anti–*Pneumocystis jiroveci* activity in nonhuman animal models; however, the corresponding human clinical experience has been rarely reported. We report a clinical picture of *P jiroveci* pneumonia (PJP) and determine the effects of concomitant therapy with echinocandins and trimethoprim (TMP)–sulfamethoxazole (SMZ).

Methods. We investigated a retrospective case series of heart transplantation (HT) recipients with PJP from July 1988 to December 2015. Recipient charts were reviewed for their demographic characteristics, underlying conditions, concomitant infections, PJP prophylaxis, TMP-SMZ dosages, adverse events, echinocandin use, oxygenation, and outcomes.

Results. Eleven of 451 HT recipients developed PJP after a median duration of 2.8 years after transplantation. All 11 were treated with TMP-SMZ; 5 of them were treated with echinocandins added to the standard TMP-SMZ regimen. The longest interval between transplantation and PJP development was 16.3 years. The mortality rate was 33.3% in recipients receiving TMP-SMZ alone, whereas it was 20% in those receiving echinocandins as well. The most common side effects of TMP-SMZ include nausea and vomiting, metabolic acidosis, and hyperkalemia. Five recipients developed acute psychosis after a median duration of 6 days of TMP-SMZ therapy. The incidence of psychosis increased from 25% in recipients receiving TMP at ≤15 mg/kg/d to 100% in those receiving TMP at >15 mg/kg/d.

Conclusions. Echinocandins along with the standard TMP-SMZ regimen may effectively alleviate PJP developed after HT. The ideal prophylaxis duration is lifelong owing to the late onset of PJP. The typically intolerable adverse effects of TMP-SMZ therapy for PJP may necessitate dosage adjustments in some cases.

In solid organ transplant recipients receiving standard immunosuppressive therapy, the incidence of *Pneumocystis jiroveci* pneumonia (PJP) is 5%–14% [1]. Higher mortality rates have been reported in individuals without human immunodeficiency virus (HIV) infection (39.4%) than in HIV-infected patients (9.6%) [2]. Trimethoprim (TMP)–sulfamethoxazole (SMZ) is the drug combination of choice for PJP treatment [1,3]. Some patients with PJP are intolerant or nonresponsive to TMP-SMZ therapy [4–6]. In a case note review of 962 cases of HIV-associated PJP treated with TMP-SMZ, therapy was changed owing to 198 (20.6%) toxicity episodes [4]. Therefore, developing alternative treatments may improve PJP outcomes.

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Pneumocystis typically exists in small trophic forms as well as larger cyst forms. Large cyst forms continuously generate new trophic forms; therefore, these forms represent a major organism reservoir [7,8]. In contrast to the trophic forms, the main structural component of the cell wall in *Pneumocystis* cysts is β-1,3-glucan [8,9]. The β-1,3-glucan synthesis inhibitors echinocandins (eg, caspofungin, micafungin, and anidulafungin) have shown anti-*P jiroveci* activity in nonhuman animal models; however, the corresponding human clinical experience has been rarely reported [7,9,10]. In humans, cell wall disruption is an attractive PJP treatment target, particularly because of the absence of glucan in human cells.

Here, we report the clinical picture of PJP among heart transplantation (HT) recipients at our heart center and determine the effects of concomitant therapy with echinocandins and TMP-SMZ on PJP treatment outcomes.

METHODS

We investigated a retrospective case series of HT recipients with PJP from July 1988 to December 2015. PJP was diagnosed using polymerase chain reaction–based *P jiroveci* detection in sputum. All infected recipients were treated with TMP-SMZ. Five were also treated with echinocandins along with the standard TMP-SMZ regimen. Patients' charts were reviewed to identify their demographic characteristics, underlying conditions, concomitant infections, PJP prophylaxis, TMP-SMZ dosages, adverse events, echinocandin use, oxygenation (ie, partial pressure of arterial oxygen/fraction of inspired oxygen [PaO_2/FiO_2]), and outcomes.

RESULTS

During the study period, orthotopic HT was performed on 451 recipients; of these, 11 (2.44%) developed PJP after HT. A review of immunosuppressive agents indicated that the combination of tacrolimus, mycophenolate, and prednisolone was the most commonly prescribed. Two recipients had been hospitalized to receive antirejection therapy 1 month before PJP development. In addition to PJP, 3 concomitant infections were detected, with cytomegalovirus infection being the most common ($n = 8$), followed by *Candida albicans* ($n = 4$) and rotavirus ($n = 1$) infections.

Five of 11 recipients took prophylactic TMP-SMZ for durations ranging from 76 to 861 days. However, when PJP developed, none of the 11 recipients were taking prophylactic TMP-SMZ. All 11 recipients eventually developed PJP after a median duration of 2.8 years after transplantation. Five patients (45%) were diagnosed with PJP within 2 years after HT, whereas the others (55%) developed PJP >2 years after of HT. The longest interval between HT and PJP development was 16.3 years. All 11 recipients were treated with TMP-SMZ at a mean TMP dosage of 11.4 mg/kg/d and a median therapy duration of 15 days (range, 6–34). Treatment of HT recipients with PJP infection is summarized in Table 1.

Echinocandins were added to the standard TMP-SMZ regimen for 5 recipients: anidulafungin in 4 and caspofungin in. The median length of the echinocandin therapy was 15 days (range, 6–19). The mortality rate was 33.3% for the 6 recipients treated with only TMP-SMZ, whereas it was 20% for the 5 recipients taking additional echinocandins. Figure 1 presents a comparison of the PaO_2/FiO_2 of the echinocandin + TMP-SMZ and TMP-SMZ–only groups. The mean PaO_2/FiO_2 on days 6 and 9 of echinocandin + TMP-SMZ versus TMP-SMZ–only therapy was 211 versus 185 mm Hg and 413 versus 224 mm Hg, respectively.

The most common side effects of TMP-SMZ were nausea and vomiting, metabolic acidosis, and hyperkalemia (Fig 2). Acute psychosis occurred in 5 recipients after receiving TMP-SMZ therapy for a median duration of 6 days (range, 3–13). The incidence of psychosis increased from 25% in recipients receiving a daily TMP dose of ≤15 mg/kg to 100% in recipients receiving a daily TMP dose of >15 mg/kg. One patient was intolerant to TMP-SMZ, as indicated by a severe cutaneous reaction that was resolved after changing TMP-SMZ to primaquine and clindamycin.

DISCUSSION

Utili et al [7] reported that in 4 transplant recipients for whom caspofungin was used as an additional drug along with the standard TMP-SMZ regimen, rapid improvement and complete alleviation were observed. In contrast, in a retrospective review, 2 leukemia patients diagnosed with PJP died despite prolonged echinocandin treatment [10]. Clinical experience of echinocandins in the treatment of PJP is rare. Table 2 summarizes the characteristics of the reported cases of echinocandin use for PJP. In our preliminary experience, the mortality rate was 33.3% for treatment with TMP-SMZ alone and, in contrast, 20% after addition of echinocandin to the regimen. The 33.3% mortality observed for TMP-SMZ alone was similar to that reported previously [2]. After 1 week of treatment, the PaO_2/FiO_2 in the echinocandin + TMP-SMZ group was greater than that in the TMP-SMZ–only group. Limitations of this retrospective study included missing data for PaO_2/FiO_2 and small sample size.

Definitive evidence for the ideal duration of PJP prophylaxis is unavailable. Experts have suggested that it should be 6 months to 1 year for kidney transplantation recipients and ≥1 year for heart, liver, intestine, and lung transplantation recipients [1,15]. Craker [16] reported a case of PJP occurring >8 years after cardiac transplantation. In the present study, the longest interval between HT and PJP development was 16.3 years. The duration of PJP prophylaxis at our heart center has been changed from ~2 years to lifelong.

The TMP-SMZ therapy for treating PJP typically has intolerable side effects, the worst of which are nausea and vomiting and acute psychosis. Saigenji et al [17] reported 5 patients with PJP developed after HT, and the identified side effects of TMP-SMZ were nausea, vomiting, and anorexia, which were presented by 4 patients (80%). Our

Table 1. Treatment of Heart Transplant Recipients With *Pneumocystis jiroveci* Pneumonia (PJP)

Patient	Age (y)	Sex	Immunosuppressive Regimen	Onset of PJP* (y)	Prophylaxis of PJP* (mo)	TMP-SMZ		Others		eGFR	Outcome (Cause Of Mortality)
						Dose of TMP (mg/kg/d)	Length of Therapy (d)	Drug and Dosage	Length of Therapy (d)		
1	55.5	Male	CsA, MMF, Pred	5.4	No	11.7	34	–	–	42.0–77.4	Alive
2	25.0	Female	CsA, MMF, Pred	9.4	No	3.7	13	Primaquine, 15 mg daily; clindamycin, 300 mg every 6 h	6	PD	Alive
3	56.0	Male	Tac, Pred	1.9	No	9.7	17	–	–	23.6–36.9	Died (ARDS)
4	57.6	Female	CsA, MPA, Pred	0.9	No	16	10	–	–	28.9–54.5	Alive
5	59.5	Male	Tac, MMF, Pred	0.4	No	14.3	6	–	–	30.7–35.5	Died (sepsis†)
6	41.4	Female	Tac, MMF, Pred	1.6	0.2–12.9	19.2	15	–	–	41.7–109.9	Alive
7	44.6	Male	Tac, MMF, Pred	2.8	0.2–22.9	8.3	23	Caspofungin, 70 mg initially, 50 mg daily	16	39.3–75.7	Alive
8	34.4	Male	Tac, MMF, Pred	4.7	20.2–43.2	20	15	Anidulafungin, 200 mg initially, 100 mg daily	15	39.7–91.7	Alive
9	71.6	Male	CsA, MMF, Pred	3.3	1.2–29.9	11	7	Anidulafungin, 200 mg initially, 100 mg daily	6	9.0–19.3	Died (sepsis†)
10	37.7	Male	Tac, MMF, Pred	0.5	0.5–3.1	6.2	22	Anidulafungin, 200 mg initially, 100 mg daily	19	12.3–16.6	Alive
11	76.1	Male	CsA, MPA, Pred	16.3	No	5.5	27	Anidulafungin, 200 mg initially, 100 mg daily	14	10.5–30.3	Alive

Abbreviations: ARDS, acute respiratory distress syndrome; CsA, cyclosporine; MMF, mycophenolate mofetil; MPA, mycophenolate sodium; Pred, prednisolone; Tac, tacrolimus.
*After heart transplantation.
†Together with multiple organ failure.

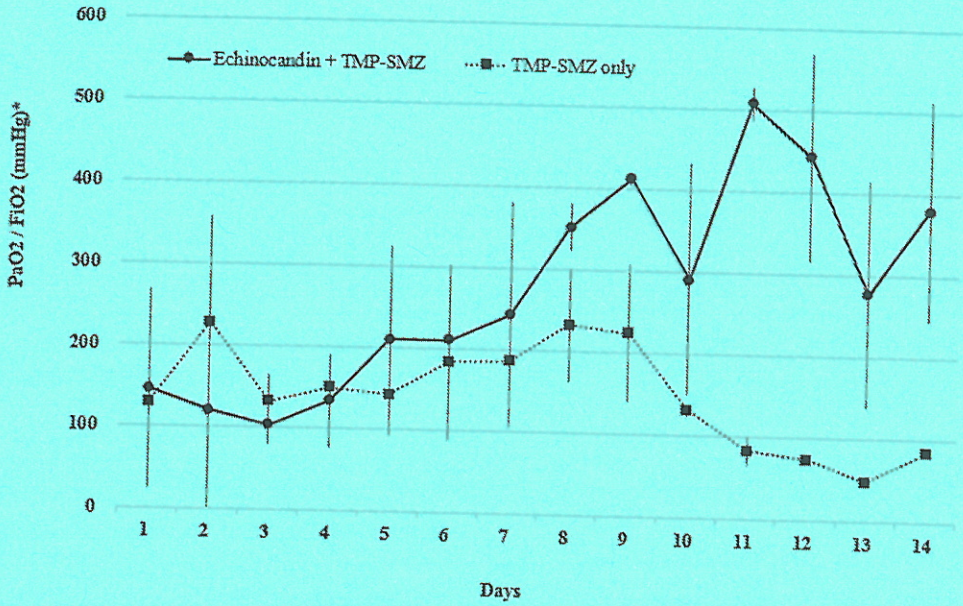

Fig 1. Daily oxygenation (PaO_2/FiO_2) in the echinocandin + TMP-SMZ and TMP-SMZ–only groups. Abbreviations: PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen. *Mean ± SD.

results corroborated this observation, with 8 of our recipients (73%) exhibiting nausea and vomiting. Furthermore, 45% of our HT recipients developed acute psychosis while receiving TMP-SMZ, a less favorable proportion compared with renal transplantation recipients (20%) [18] and HIV-infected patients (11.9%) [19]. Here, the onset of psychosis symptoms occurred after 6 days (range, 3–13) of TMP-SMZ use. Similarly, for renal transplantation recipients and HIV-infected patients, the intervals were 3 days (range, 2–10) [18] and 5 days (range, 3–11) [19], respectively. The incidence of psychosis increased from 25% in recipients receiving a daily TMP dose of ≤15 mg/kg to 100% in recipients receiving a daily TMP dose of >15 mg/kg. Thus, acute psychosis was a dose-related side effect, an observation corroborated by Lee et al [19].

The TMP dosage recommendation for PJP treatment, established by Hughes et al [20], is 20 mg/kg/d; those authors had prescribed it for pediatric oncology patients and then extrapolated it to adult patients [21]. Dose per weight, however, is higher in children than in adults for achieving similar peak levels of TMP-SMZ [22]. Excessive drug concentrations may be consumed in cases where adult patients are treated with an extrapolated mg/kg dose for children. Intolerable adverse effects occurred when the

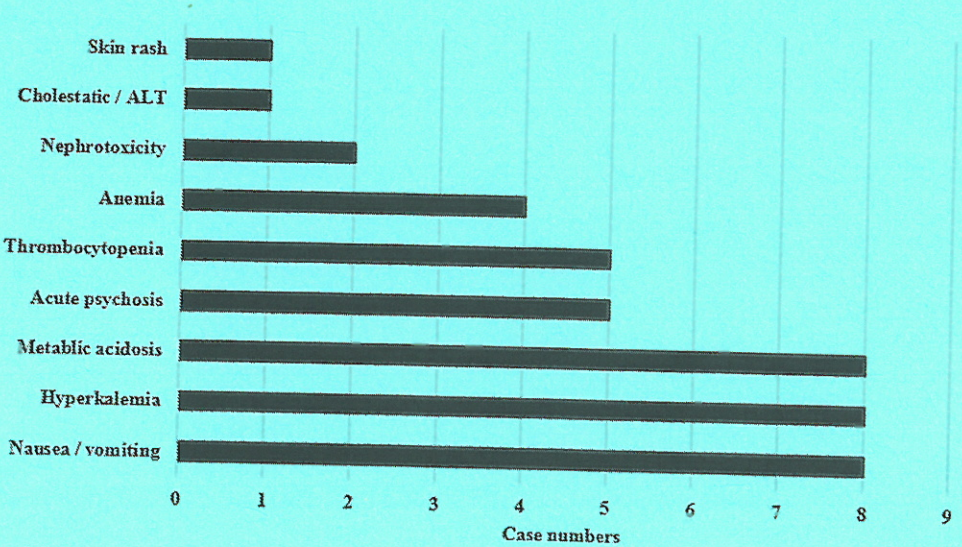

Fig 2. Adverse effects associated with high-dose TMP-SMZ therapy. Abbreviation: ALT, alanine transaminase.

Table 2. Clinical Characteristics of the Reported Cases of Echinocandins Use for *Pneumocystis jiroveci* Pneumonia

Author	Cases	Age (y)	Sex (M/F)	Underlying Conditions	Treatment Regimen	Length of Echinocandin Therapy (d)	Outcome
Kim et al [6]	4	1, 46, 57, 63	4/0	SCID: 1 Liver transplant: 2; Kidney transplant: 1	TMP-SMZ + caspofungin	4–25	Alive: 1; Died: 3
Utili et al [7]	4	28, 57, 58, 59	2/2	Renal transplant: 2; Heart transplant: 2	TMP-SMZ + caspofungin	7–16	Alive: 4
Kamboj et al [10]	2	13, 42	1/1	Lymphocytic leukemia: 1; Stem cell transplant: 1	TMP-SMZ + micafungin: 1 pentamidine + caspofungin: 1	18–30	Died: 2
Tu et al [11]	3	35, 43, 61	3/0	Renal transplant: 3	TMP-SMZ* + caspofungin	14	Alive: 2; Died: 1
Annaloro et al [12]	1	45	1/0	Bone marrow transplant	TMP-SMZ + caspofungin	45	Alive: 1
Hof et al [13]	1	60	1/0	Wegener granulomatosis	Caspofungin	>21	Alive: 1
Ceballos et al [14]	1	39	1/0	HIV	TMP-SMZ + caspofungin	NA	Alive: 1

Abbreviations: HIV, human immunodeficiency virus; SCID, severe combined immune deficiency; TMP-SMZ, trimethoprim-sulfamethoxazole.
*Low-dose.

aforementioned recommended dosages were prescribed to healthy adults [21]. The present study showed similar negative results when 15–20 mg/kg/d TMP-SMZ, adjusted according to the patient's renal function, was used to treat HT recipients. To reduce the likelihood of severe toxicity, Sattler et al [23] argued that the TMP-SMZ dosage should be adjusted to maintain serum TMP concentrations at 5–8 μg/mL. Consequently, the required dosage was adjusted to 12 ± 2.7 mg/kg/d for retaining the efficacy similar to that of the conventional method [23]. Tu et al [11] reported 3 cases of severe PJP in renal transplantation recipients treated with a combination of caspofungin and low-dose TMP-SMZ. The combined treatment potentially alleviated PJP and reduced the incidence of TMP-SMZ–related adverse effects [11].

CONCLUSION

Echinocandins along with the standard TMP-SMZ regimen are potentially useful for effective alleviation of PJP after HT. The ideal duration of prophylaxis can be lifelong owing to the late onset of PJP after HT. Dosage adjustments may be required to minimize the typical intolerable adverse effects of TMP-SMZ therapy for PJP.

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