Combination of Clindamycin and Primaquine for *Pneumocystis* Pneumonia in Renal Transplant Recipients

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Abstract

Pneumocystis pneumonia (PCP) in kidney transplant recipients is usually treated with trimethoprim-sulfamethoxazole (TMP-SMX). Combination of clindamycin and primaquine (C + P) is recommended for treatment failure. Data are scarce for treatment with C + P in renal transplant recipients. Here, we present three kidney transplant recipients on triple immunosuppression (tacrolimus, mycophenolate mofetil, and prednisolone) diagnosed to have PCP at different time periods after transplant surgery. Bronchoscopy and lavage were done; special staining with Gomori methenamine silver stain demonstrated *Pneumocystis jirovecii*. Two patients had graft dysfunction at the time of diagnosis. The first patient was started on TMP-SMX but developed leukopenia and was started on oral C + P. The other two cases had graft dysfunction and were started on C + P. All responded to therapy without complications, and improvement in graft function was observed. Clindamycin with primaquine can be considered as a safe and effective option to treat PCP in renal transplant recipients; this combination can replace TMP-SMX, as the first-line therapy, especially in patients with graft dysfunction or leukopenia

Keywords: Clindamycin, *Pneumocystis* pneumonia, posttransplant infection, primaquine, trimethoprim-sulfamethoxazole

Introduction

Pneumocystis jirovecii is an opportunistic fungal pathogen that causes life-threatening infection in immunocompromised individuals. The incidence of *Pneumocystis* pneumonia (PCP) among solid-organ transplant recipients ranges from 5% to 15%, depending on the organ transplanted and the immunosuppressive drug regimen used. In kidney transplant recipients, the reported incidence is 0.4–2.7/1000 patient-years.[1] *Pneumocystis jirovecii* pneumonia commonly occurs in the first 2–6 months after transplantation. The first-line drug for treatment is trimethoprim-sulfamethoxazole (TMP-SMX). Alternative drugs, also called the second-line drugs, include intravenous pentamidine, dapsone, and combination of clindamycin and primaquine (C + P).[2]

Case Report

We report three kidney transplant recipients presenting with fever for evaluation, at different time periods after transplantation. At our center, all transplant recipients receive TMP-SMX for the first 6 months. Clinical characteristics of all three patients are summarized in Table 1 and laboratory parameters are summarized in Table 2. All were on maintenance immunosuppression (tacrolimus [0.1 mg/kg/day], mycophenolate mofetil [1 g twice daily], and prednisolone [0.5 mg/kg/day, tapered to 5 mg/day in 3 months]); tacrolimus levels after 3 months were targeted between 4 and 6 ng/ml. Patient 1 underwent second kidney transplantation and he was given antithymocyte globulin (ATG) along with three sessions of plasma exchange before transplant, as the donor-specific antibody was positive. Patient 2 had acute cellular rejection at 10 months after transplant and had received three doses of intravenous methyl prednisolone (500 mg). Blood sugars were normal in all. X-ray chest [Figure 1a-c] was abnormal in Patient 1, but near normal in Patients 2 and 3. There was poor correlation with high-resolution computed tomography (HRCT)

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chest findings, which showed bilateral extensive ground-glass opacities [Figure 2a-c]. Bronchoscopy and bronchoalveolar lavage (BAL) were done in all patients and subjected to special stain (Gomori methenamine silver [GMS]), which confirmed PCP [Figure 3]. Patient 1 was started on TMP-SMX (Dose: TMP: 15–20 mg/kg/day and SMX: 75–100 mg/kg/day); he developed severe leukopenia; the drug was discontinued and was started on oral C + P. Patients 2 and 3 had renal insufficiency. They were treated with oral clindamycin (600 mg, thrice daily) + primaquine (30 mg, once daily) for 21 days as the first-line therapy. Adjunctive prednisolone was also given for 3 weeks; 40 mg twice daily for 5 days, followed by 40 mg daily for 5 days and then 20 mg daily for 11 days. The dose of mycophenolate mofetil was also reduced.

All three patients tolerated the medications and had complete resolution of symptoms in 3 weeks. Clinical characteristics after treatment are summarized in Table 3. Imaging of chest showed complete resolution of lesions [Figure 4a-c]. No adverse effects were noted with C + P combination therapy.

Discussion

PCP is an opportunistic infection that typically presents in the first 6 months after renal transplantation, with fever, nonproductive cough, effort intolerance, low oxygen saturation, and diffuse interstitial infiltrates on radiograph of the chest. All three of our patients had fever and cough; two of them had low oxygen saturation on presentation. Two patients

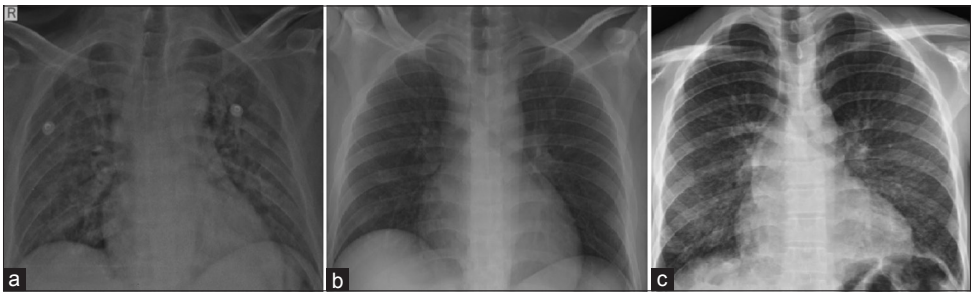

Figure 1: X-ray chest at diagnosis (a: Patient 1) Diffuse reticulonodular shadowing (b: Patient 2) Prominent bronchovascular markings in bilateral hilar regions (c: Patient 3) Prominent bronchovascular markings

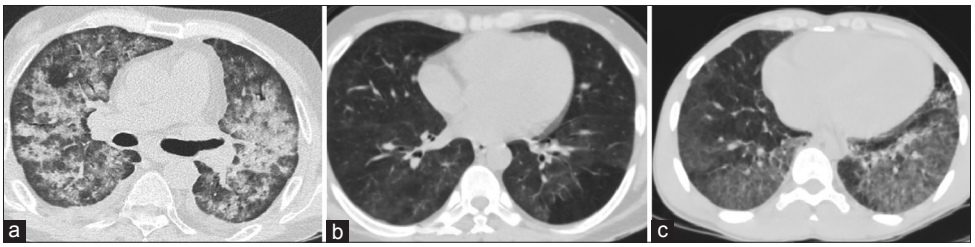

Figure 2: High-resolution computed tomography chest at diagnosis (a: Patient 1) Bilateral alveolar ground-glass and dense opacity in the upper and middle lobes (b: Patient 2) Multiple ground-glass nodules in all lobes, more in the right upper and lower lobes (c: Patient 3) Bilateral diffuse ground glassing with reticular septal thickening

Table 1: Demographic and clinical characteristics

Characteristics	Patient 1	Patient 2	Patient 3
Age (years)	52	26	19
Gender	Male	Male	Male
Duration after transplantation	4 months	1 year	8 years
Donor	Wife	Mother	Father
Induction	Antithymocyte globulin (second transplant)	Nil	Nil
Plasma exchange before transplant	three sessions (donor-specific Class I antibody)	Nil	Nil
Maintenance immunosuppression	Tacrolimus mycophenolate mofetil prednisolone	Tacrolimus mycophenolate mofetil prednisolone	Tacrolimus mycophenolate mofetil prednisolone
Acute rejection episodes	Nil	Yes (treated with three doses of methyl prednisolone)	Nil
Clinical features	Fever, dry cough, and dyspnea	Fever, productive cough, and dyspnea	Fever, dry cough, and backache
SpO_2 at room air (%)	75	90	95
Ventilatory support	Noninvasive	No	No

SpO_2: Oxygen saturation

developed PCP in the 1st year after transplant and the third patient developed after 8 years.

Risk factors for PCP include use of ATG, corticosteroids, mycophenolate mofetil, calcineurin inhibitors, cytomegalovirus disease, low CD4+ T cell counts, neutropenia, and most importantly exposure to patients with PCP. ATG induction has been reported to be the highest risk factor for PCP,[2] as seen in our first patient who developed infection in spite of receiving PCP prophylaxis. In our institute, we give PCP prophylaxis with TMP-SMX for all kidney transplant recipients for the first 6 months after renal transplantation. Other risk factors include use of antirejection therapy,[3] as seen in our second patient, who had received three doses of intravenous methyl prednisolone.

HRCT scans are more sensitive than radiograph of the chest and may show ground-glass opacities with sparing of lung periphery;[4] this was noted in our cases, where two patients had near-normal X-ray chest and HRCT chest was clearly abnormal. BAL microscopy and staining is a highly sensitive method of diagnosing PCP and has a yield of 80%.[2] All the three cases underwent BAL with special staining with GMS stain, which can identify cell wall of the cysts.[2] In all three cases, GMS stain was positive and diagnosis was established by demonstrating the organism; polymerase chain reaction (PCR) was positive for *Pneumocystis jirovecii*. PCR with sputum and BAL fluid samples have a high sensitivity and specificity for the detection of the organism, but lacks utility in diagnosing PCP, as PCR cannot differentiate colonization from infection. However, PCR has a negative predictive value of 100%.[1]

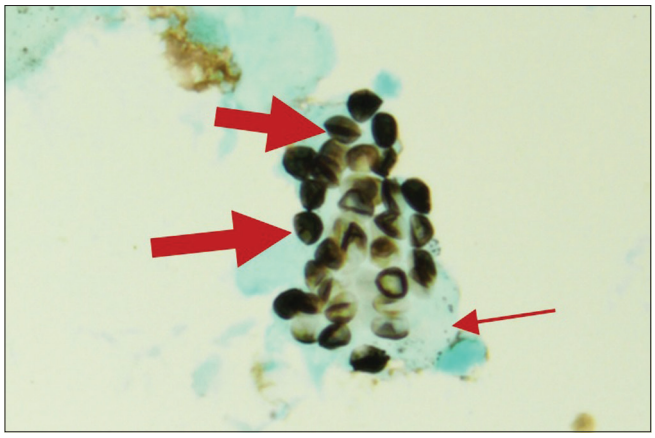

Figure 3: Bronchoalveolar lavage fluid: Gomori methenamine silver stain: stained cyst walls (thick arrow); alveolar cast (thin arrow); organisms appear as folded spears

TMP-SMX is the first-line agent and is quoted as the drug of choice.[5] No agent has been shown to have a superior outcome. Patient 1 was started on therapeutic dose of TMP-SMX; there was a fall in total leukocyte count, TMP-SMX was stopped, and he was started on oral C + P. Leukopenia is a known complication of TMP-SMX, risk is higher when used in combination with an antimetabolite; TMP-SMX causes a dose-dependent leukopenia,[6] and a high dose of TMP-SMX (TMP: 15–20 mg/kg/day and SMX: 75–100 mg/kg/day) is recommended for treating PCP; however, there is no reported risk of leukopenia with C + P. TMP-SMX is associated with thrombocytopenia as well; generation of antibodies to glycoprotein IIb/IIIa complex on platelets can cause immune thrombocytopenia which is most commonly seen in within 1st week of treatment and is reversible on stopping the drug,[6] there is no risk for thrombocytopenia with C + P. Hyperkalemia is also seen in 6% of patients receiving TMP-SMX;[6] however, incidence can go up to 50% in those with graft dysfunction.[7] In

Table 2: Investigations (at admission)

	Patient 1	Patient 2	Patient 3
Hemoglobin (g/dl)	9.3	8.3	8.6
Total leukocyte count (per cumm)	5700	14,400	5600
Platelet count (per cumm)	184,000	301,000	281,000
Serum creatinine (mg%)	0.98	4.56	3.02
HbsAg; HCV; HIV	Negative	Negative	Negative

HCV: Hepatitis C virus, HbsAg: Hepatitis B surface antigen

Table 3: Clinical and diagnostic parameters after treatment (after 3 weeks of C + P)

	Patient 1	Patient 2	Patient 3
Clinical improvement	Complete	Complete	Complete
SpO_2 at room air (%)	99	99	100
Repeat HRCT chest	Normal	Normal	Normal
Hemoglobin after treatment (g/dl)	12.4	11.5	10.2
Serum creatinine (mg) (%)	0.84	3.99	2.04
Adverse effects of drugs	Nil	Nil	Nil

HRCT: High-resolution computed tomography, SpO_2: Oxygen saturation, C + P: Clindamycin and Primaquine

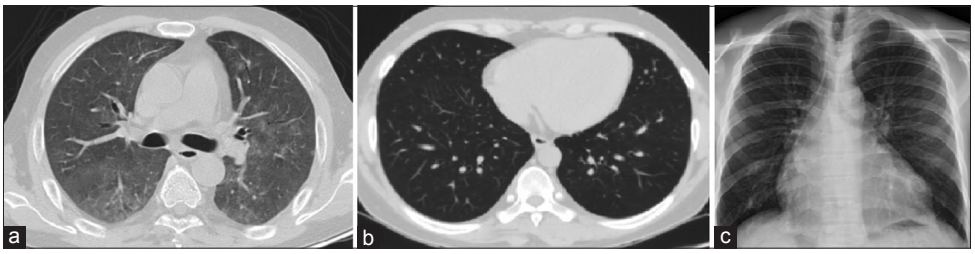

Figure 4: Imaging after 3 weeks of treatment with C + P (a: Patient 1) improved significantly (b: Patient 2) normal (c: Patient 3) normal

Patient 2, there was moderate renal failure (serum creatinine: 4.56 mg%), renal dose modification is needed for TMP-SMX and requires drug level monitoring.[6] Therefore, TMP-SMX was not considered and he was started on oral C + P. There is no need for dose modification and drug level monitoring for C + P. Patient 3 also had graft dysfunction and was started on oral C + P. There is a consensus for adjunctive steroid therapy in HIV-infected patients,[8] the dose recommended was used in our patients for 3 weeks, which they tolerated well.

All three patients showed clinical improvement and recovered completely**.** Oral therapy with C + P is adequate because the oral bioavailability of clindamycin is 90% and primaquine is 96%. Moreover, primaquine is not available in parenteral form; however, we agree parenteral clindamycin can be considered to have an edge over the oral regimen. Graft functions showed an improvement. No adverse effects of the drugs were noted. There are no drug interactions of C + P with tacrolimus and mycophenolate mofetil. Most of the data on C + P for treatment of PCP comes from HIV-infected patients. The first study done exclusively in renal transplant recipients to assess TMP-SMX versus C + P for treatment of PCP was reported in 2014.[9] The failure rate of TMP-SMX was more than C + P group, and half of the treatment failure in TMP-SMX group were attributed to adverse drug effects; no adverse drug effects were seen in the C + P group.[9] An Indian study also reported, adverse effects of TMP-SMX was seen in 44% of patients; they were eventually switched over to C+P;[7] the authors reported that superiority of TMP-SMX in the treatment of PCP compared to C + P is marginal.[7,9]

Conclusion

PCP in kidney transplant recipients can be safely and effectively treated with C + P, without any major drug-related side effects. There is need for further studies to conclude if C + P is noninferior to TMP-SMX in renal transplant recipients with graft dysfunction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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