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No Recurrence of *Pneumocystis jirovecii* Pneumonia after Solid Organ Transplantation Regardless of Secondary Prophylaxis

Tark Kim,[a] Heungsup Sung,[b] Yu-Mi Lee,[a] Hyo-Lim Hong,[a] Sung-Han Kim,[a] Sang-Ho Choi,[a] Jun Hee Woo,[a] Yang Soo Kim,[a] and Sang-Oh Lee[a]

Departments of Infectious Diseases[a] and Laboratory Medicine,[b] Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

There are no data on the efficacy of secondary prophylaxis against *Pneumocystis* pneumonia after solid organ transplantation. Therefore, we investigated the rate of recurrence of *Pneumocystis* pneumonia after solid organ transplantation in a retrospective cohort study. Between 2005 and 2011, a total of 41 recipients recovered from *Pneumocystis* pneumonia. Of these, 22 (53.7%) received secondary prophylaxis. None of the 41 recipients experienced recurrence of *Pneumocystis* pneumonia during the follow-up, regardless of secondary prophylaxis.

Pneumocystis jirovecii pneumonia (PcP) is one of the main opportunistic infections of immunocompromised patients (14, 15). It was found to have the highest incidence (4.7 cases/100 person years) among opportunistic infections in HIV-infected patients (5), and its overall prevalence in solid organ transplant (SOT) recipients was 5 to 10% (14). To reduce adverse outcomes related to PcP, primary prophylaxis is usually recommended for both HIV-infected patients (15) and SOT recipients (8).

Secondary prophylaxis is also recommended for HIV-infected patients, using the same criteria as for primary prophylaxis (15), because without secondary prophylaxis, PcP frequently recurs; the cumulative rate has been reported to be 50% by 24 weeks (9). For SOT recipients, life-long secondary prophylaxis is suggested by some experts (8), since immunosuppressants are required throughout their lives. However, no recent data are available on how many recipients experience recurrence of PcP after a SOT is received. We therefore examined the rates of recurrence of PcP in SOT recipients with and without secondary prophylaxis.

Patients and methods. This study was performed retrospectively at the Asan Medical Center, a 2,700-bed tertiary-care teaching hospital in Seoul, South Korea. By searching electronic medical records, we established a cohort of patients diagnosed with PcP between January 2005 and December 2011. Patients under 16 years of age were excluded. After reviewing underlying conditions and clinical outcomes, we included in the analysis only SOT recipients who had recovered from PcP.

Data on demographics, type of organ and donor, immunosuppressants before PcP, onset time of PcP after transplantation, initial severity of PcP (12), and adjunctive corticosteroid use (16) were collected. The follow-up duration was determined by subtracting the date when PcP treatment was last given from the date of last attendance at the outpatient clinic or of death. For patients who underwent graftectomy for any reason, the last follow-up date was defined as the date of graftectomy. During the follow-up period, data on acute rejection, immunosuppressant use after PcP, regimen and duration of secondary prophylaxis, graft failure, and recurrence of PcP were collected. Serum tacrolimus and cyclosporine levels at the time of PcP diagnosis and 6 months after PcP were compared using the Wilcoxon signed-rank test. Clinical variables of recipients with and without secondary prophylaxis were compared; categorical variables were compared by Fisher's exact test, and continuous variables were compared by the Mann-Whitney U test.

Results. We identified a total of 53 SOT recipients with PcP confirmed by direct immunofluorescence assay (Light Diagnostics Pneumocystis carinii DFA kit; Millipore, Billerica, MA) using bronchoalveolar lavage specimens. Of these, 41 (77.4%) recovered from PcP, and of the latter, 22 received trimethoprim-sulfamethoxazole (21, 95.5%) or dapsone (1, 4.5%) for secondary prophylaxis. The median duration of the secondary prophylaxis was 4 months (interquartile range [IQR], 5 to 7 months).

The median follow-up duration was 21 months (IQR, 9 to 48 months), 6 months (IQR, 16 to 48 months) for recipients who received secondary prophylaxis and 29 months (IQR, 11 to 58 months) for those who did not. During the follow-up period, PcP did not recur in any of the patients whether or not they received secondary prophylaxis. The most common immunosuppressant regimen used both before PcP (20/41. 48.8%) and after PcP (14/41, 34.1%) was tacrolimus plus mycophenolate mofetil. The median serum immunosuppressant levels were higher at the time of PcP diagnosis than at 6 months after PcP: 8.2 (IQR, 6.4 to 15.3) versus 7.0 (IQR, 4.3 to 7.9) ng/ml for tacrolimus ($P = 0.01$) and 167 (IQR, 121 to 239) versus 114 (IQR, 62 to 165) ng/ml for cyclosporine ($P = 0.03$). The median corticosteroid (prednisone) dose was 7.5 (IQR, 6.3 to 10) mg at the time of PcP diagnosis, and 29.3% (12/41) of the patients had episodes that required more than 20 mg of prednisone. The median absolute lymphocyte counts at the time of PcP diagnosis and nadir absolute lymphocyte counts were 810 (IQR, 383 to 1,208)/μl and 1,238 (IQR, 733 to 1,884)/μl, respectively. Five (12.2%) recipients experienced acute rejection during the follow-up period. The clinical characteristics of those recipients who received secondary prophylaxis did not differ from those who did not (Table 1).

Discussion. No recurrence of PcP was observed in SOT recip-

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Address correspondence to Sang-Oh Lee, soleemd@amc.seoul.kr.

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TABLE 1 Comparison of clinical characteristics of solid organ transplant recipients who did and did not receive secondary prophylaxis after recovery from *P. jirovecii* pneumonia

Clinical variable	With secondary prophylaxis ($n = 22$)	Without secondary prophylaxis ($n = 19$)	*P* value
Median age, yr (IQR)	45 (36–55)	45 (37–55)	0.65
No. (%) of males	16 (72.7)	10 (52.6)	0.21
No. (%) who received:			
Kidney	13 (59.1)	16 (84.2)	0.10
Liver	3 (13.6)	2 (10.5)	1.00
Heart	3 (13.6)	1 (5.3)	0.61
Other organ	3[a] (13.6)	0 (0)	0.24
No. (%) with a living related donor	9 (40.9)	8 (42.1)	0.34
No. (%) who received an immunosuppressant(s) before PcP development			
Tacrolimus + MMF[h]	8 (36.4)	12 (63.2)	0.12
Cyclosporine + MMF	10 (45.5)	4 (21.1)	0.19
Tacrolimus only	2 (9.1)	2 (10.5)	1.00
Other	2[b] (9.1)	1[c] (5.3)	1.00
No. (%) who received an immunosuppressant(s) after PcP treatment			
Tacrolimus + MMF	7 (31.8)	7 (36.8)	0.76
Cyclosporine + MMF	7 (31.8)	3 (15.8)	0.29
Tacrolimus only	5 (22.7)	4 (21/1)	1.00
Other	3[d] (13.6)	5[e] (26.3)	0.44
Median ALC[i]/μl (IQR)			
At time of PcP diagnosis	673 (385–1,146)	833 (327–1,387)	0.44
Nadir after primary PcP	1,236 (740–2,257)	1,238 (721–1,734)	0.68
Median onset time (mo) of PcP from transplantation (IQR)	10 (6–13)	15 (6–30)	0.37
No. (%) with initial severity of PcP at diagnosis[f]			
Mild	6 (27.3)	7 (36.8)	0.74
Moderate to severe	16 (72.7)	12 (63.2)	0.74
No. (%) with adjunctive corticosteroid use[g]	13 (59.1)	9 (47.4)	0.75
No. (%) with secondary prophylaxis regimen			
TMP-SMX[j]	21 (95.5)	NA[k]	NA
Dapsone	1 (4.5)	NA	NA
Median duration (mo) of secondary prophylaxis (IQR)	4 (5–7)	NA	NA
Median follow-up duration, mo (IQR)	6 (16–48)	29 (11–58)	0.29
No. (%) with graft failure during follow-up period	3 (13.6)	6 (31.6)	0.70
No. (%) with recurrence of PcP	0	0	NA

[a] Two simultaneous kidney-pancreas transplants, one pancreas transplant.
[b] Cyclosporine only and cyclosporine plus everolimus.
[c] Sirolimus only.
[d] Two tacrolimus plus azathioprine, one cyclosporine plus everolimus.
[e] Three cyclosporine only, one tacrolimus plus azathioprine, one sirolimus.
[f] Severity of PcP was based on partial arterial oxygen pressure while breathing room air or on the alveolar-arterial oxygen difference as previously defined (12).
[g] Use of adjunctive corticosteroid as previously defined (16).
[h] MMF, mycophenolate mofetil.
[i] ALC, absolute lymphocyte count.
[j] TMP-SMX, trimethoprim-sulfamethoxazole.
[k] NA, not applicable.

ients, regardless of secondary prophylaxis. To our knowledge, this is the first study of the rate of recurrence of PcP in SOT recipients and the efficacy of secondary prophylaxis.

The administration of a regimen as secondary prophylaxis against PcP is generally recommended in HIV-infected patients (4). All patients with previous episodes of PcP should receive secondary prophylaxis, because without it the recurrence rate is very high (9). The criteria for discontinuing secondary prophylaxis are the same as those for primary prophylaxis (4); observational studies support the consensus that secondary prophylaxis can be discontinued when HIV-infected patients respond to antiretroviral therapy and their CD4 cell counts remain above 200/mm^3 for 3 months (6, 10).

On the other hand, there is no clear consensus about which SOT patients should receive secondary prophylaxis or how long they should receive it. Since SOT recipients need to take immu-

nosuppressants as long as their transplants are in place, it seems possible for PcP to develop at any time. Indeed, 36% of PcP episodes were found to occur more than a year after a SOT was received (3). In addition, Trimethoprim-sulfamethoxazole, most commonly used for PcP prophylaxis, can also prevent other opportunistic infections such as nocardiosis and toxoplasmosis. On that basis, some experts advise life-long secondary prophylaxis (8).

However, contrary to this viewpoint, we failed to discover any recurrence of PcP in our study. One reason for this result may be the fact that our clinicians tried to lower serum immunosuppressant levels and tended to switch from tacrolimus plus mycophenolate mofetil, which are known to increase the risk of PcP (2, 7), to other immunosuppressants (tacrolimus only for five patients, tacrolimus plus azathioprine for one patient). However, it is not certain that the absence of recurrence of PcP was associated with less mycophenolate use after PcP, because there are studies suggesting antipneumocystis activity of mycophenolate (1, 11). Also, acute rejection, an important risk factor for PcP in SOT recipients (13), did not occur frequently in our patients. Nonrecurrence of PcP might not be the case in other hospitals that perform SOTs, since the rate of acute rejection could differ between hospitals. That is why multicenter studies should be performed to make a new strategy for secondary prophylaxis of SOT recipients. Finally, nonrecurrence of PcP in our study might be associated with the type of organ transplanted and the onset time of the initial PcP; most of the recipients (70.7%) had received kidney transplants, and their median PcP onset time was about 1 year. It was reported that PcP rarely occurs more than a year after kidney transplantation (0.5 episode per 1,000 persons) (3). On the basis of this report, one might anticipate that recurrence of PcP would also be unlikely more than a year after kidney transplantation. Therefore, we propose that whether or not to recommend secondary prophylaxis for PcP in SOT recipients should be decided on a case-by-case basis, depending on the immune status of the recipient and the type of organ transplanted.

In conclusion, it seems that recurrence of PcP in SOT recipients is rare. The previous expert recommendation of life-long secondary prophylaxis for PcP in SOT recipients should be reevaluated by multicenter studies addressing the rates of other opportunistic infections, as well as the rate of PcP recurrence.

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