

Aggressive Immunosuppressant Reduction and Long-Term Rejection Risk in Renal Transplant Recipients with *Pneumocystis jiroveci* Pneumonia

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Abstract

Objectives: *Pneumocystis jiroveci* pneumonia is a rare but lethal complication in renal transplant recipients. Dose reduction of immunosuppressive agents in such situations is recommended, but its quantity and safety are unclear.

Materials and Methods: From January 2001 to January 2011, twenty of one thousand forty-six renal transplant recipients in a single center developed *Pneumocystis jiroveci* pneumonia, which was diagnosed by the Giemsa and Gomori methenamine silver stains from a specimen of bronchoalveolar lavage.

Results: We found that timing of the first immunosuppressant reduction of the *Pneumocystis jiroveci* pneumonia survivor (mean, 1.4 days after admission) was significantly earlier than that of the deceased patient (mean, 5.1 days after admission). Logistic regression analysis indicated that for those whose immunosuppressants were reduced more aggressively (either 1 of the immunosuppressants was reduced by more than 50% within 2 days of hospitalization) were significantly more likely to survive (mortality risk, OR, 0.074 [95% CI, 0.01-0.84]; $P = .035$). In addition, none of the survivors developed acute rejection or allograft necrosis during a mean follow-up of 2 years.

Conclusions: Dosage reduction of immunosuppressive agents in renal transplant recipients

with *Pneumocystis jiroveci* pneumonia should be prompt and sufficient. Aggressive immunosuppressant dosage reduction is safe in such circumstance and is associated with minimal risk of in-hospital and long-term acute allograft rejection.

Key words: *Pneumocystis jiroveci* pneumonia, Immunosuppressants, Outcomes, Rejection, Kidney transplant

Introduction

Pneumocystis jiroveci is a ubiquitous fungal pathogen worldwide. Immunocompromised patients including renal transplant recipients (RTRs) are at risk for infection with *Pneumocystis jiroveci* pneumonia (PJP). Although the routine use of PJP chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) in posttransplant period of the first 3 to 6 months,¹⁻⁴ PJP cannot be completely prevented.^{5,6}

The disease course of PJP is extremely rapid and overwhelming, and its recovery depends on early diagnosis and prompt treatment.⁷ *Pneumocystis jiroveci* mortality in RTRs is high despite aggressive treatment, and it has been reported to be between 27% and 50%.^{3,8} To improve outcomes of RTRs, previous studies have identified PJP risk factors in RTRs including poor renal function, prior allograft rejection, mycophenolate mofetil use, and persistent lymphocytopenia.⁹⁻¹¹ Moreover, to reduce PJP mortality rate in RTRs, it is crucial to identify determinants of PJP mortality that have not been investigated before. Meanwhile, for patients with PJP, KDIGO recommends reducing the amount of immunosuppressive medications.^{12,13} Nevertheless, optimal timing and quantity of dosage reduction are unknown and deserve investigation.

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We reasoned that in such an immunocompromised status, dosage reduction of the immunosuppressant should be prompt and sufficient enough. Therefore, we aimed to quantify the adequate timing and degree of immunosuppressant dosage reduction that leads to better pneumonia survival. Furthermore, we also examined long-term outcomes in *PJP* survivors.

Materials and Methods

Study protocol and subjects

From January 2001 to January 2011, there were 1146 renal transplant patients followed-up at the Taipei Veterans General Hospital, a tertiary-care referral hospital. *Pneumocystis jiroveci* chemoprophylaxis (80/400 mg/d) was routinely administered in the first 6 months after kidney transplant. Twenty of them developed *PJP* infection and the incidence was 1.7%. *Pneumocystis jiroveci* infection was diagnosed by bronchoalveolar lavage performed by chest physicians. The bronchoalveolar lavage specimens were sent for Giemsa and Gomori's methenamine silver stains. The demographic features and clinical parameters, including age, sex, comorbidities, symptoms at presentation, concomitant pulmonary infection, infection severity (eg, Acute Physiology and Chronic Health Evaluation II [APACHE II] score on the admission day), laboratory data, and patient outcomes were recorded. Estimated glomerular filtration rate (eGFR) was calculated by the simplified Modification of Diet in Renal Disease formula. Absolute neutrophil count was calculated by total white blood cell count multiplied by neutrophil percentage. Absolute lymphocyte count was calculated by total white blood cell count multiplied by lymphocyte percentage. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. The need for informed consent was waived because of the retrospective nature of the study.

Immunosuppressant regimens

Immunosuppressant regimens of patients consisted of oral corticosteroids, tacrolimus, cyclosporine, mycophenolate mofetil, and sirolimus. Because of the retrospective nature of our study, the choice and dosage of immunosuppressants were at the discretion of each nephrology attending physician. The daily

dosage, treatment duration, and dosage adjustment of each immunosuppressant agent were collected.

Management of *Pneumocystis jiroveci* pneumonia infection

Pneumocystis jiroveci pneumonia patients were diagnosed and treated aggressively. Standard *PJP* treatment protocol including intravenous high-dose TMP-SMX (TMP 15-20 mg/kg/d, adjusted according to eGFR) and corticosteroids were initiated timely, even before the bronchoalveolar lavage examination when suspicious clinically. Concomitant broad-spectrum antibiotics, mechanical ventilation, and hemodialysis and/or continuous renal replacement therapy were applied timely if indicated.

Statistical analyses

The chi-square or Fisher exact test was used to compare categorical variables, as appropriate. Continuous variables were compared by the *t* test. Values of continuous variables are presented as means and standard deviation, unless otherwise specified. The logistic regression analysis was used to determine the significance of variables in predicting short-term outcome and in-hospital mortality owing to *PJP* infection. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 15.0, IBM Corporation, Armonk, New York, USA). All probabilities were 2-tailed, and a value for $P < .05$ was considered significant.

Results

Baseline characteristics of study subjects

Table 1 shows the baseline characteristics of the 20 patients (mean age, 55 y; male, 45%; 30% had diabetes mellitus). The average time of *PJP* onset was 2.7 years after kidney transplant. A total of 16 patients (80%) had fever at presentation, 14 patients (70%) had dyspnea, 12 patients (60%) had cough, 9 patients (45%) had scanty sputum, and 2 patients (10%) had hemoptysis. There were no differences in symptoms between living or dead patients, except that dead RTRs were significantly more likely to have dyspnea at presentation than those who survived ($P = .011$).

Among patients with *PJP* development ($n=20$), 5 patients had concurrent pulmonary infection with *Pseudomonas aeruginosa* (25%), 6 had *Acinetobacter baumannii* (30%), and 3 had *Enterobacteriaceae spp.*

Table 1. Demographic Characteristics Between *PJP* Living (n=10) and Dead Patients (n=10)

	All	Living	Dead	P Value
Patient number (n)	20	10	10	
Age (y)	54.5 ± 13.0	51.0 ± 15.0	58.1 ± 10.2	.232
Sex (male %)	45.0	50.0	40.0	1.000
Comorbidities				
Diabetes mellitus (%)	30.0	30.0	30.0	1.000
Hypertension (%)	80.0	70.0	90.0	.582
Congestive heart failure (%)	10.0	0.0	20.0	.474
Coronary artery disease (%)	10.0	10.0	10.0	1.000
Symptoms at presentation				
Fever (%)	80.0	60.0	100.0	.087
Dyspnea (%)	70.0	40.0	100.0	.011*
Cough (%)	60.0	60.0	60.0	1.000
Scanty sputum (%)	45.0	50.0	40.0	1.000
Hemoptysis (%)	10.0	10.0	10.0	1.000
Concomitant pulmonary infection				
<i>Pseudomonas aeruginosa</i> (%)	25.0	10.0	40.0	.303
<i>Acinetobacter baumannii</i> (%)	30.0	20.0	40.0	.628
<i>Enterobacter</i> (%)	15.0	20.0	10.0	1.000
Infection severity				
Bacteremia	15.0	0.0	30.0	.211
Inotropic agent use	55.0	10.0	100.0	< .001*
Concomitant urinary tract infection	45.0	40.0	50.0	1.000
APACHE II score at admission	18.3 ± 5.8	17.5 ± 6.5	19.1 ± 5.3	.554
Laboratory data at admission				
Albumin (g/L)	33 ± 4	34 ± 4	32 ± 3	.453
Creatinine (μmol/L)	291.7 ± 176.8	300.6 ± 185.6	274.0 ± 159.1	.676
eGFR (mL/min)	29.2 ± 21.9	28.7 ± 20.5	29.7 ± 24.4	.924
ANC (× 10 ⁹ /L)	7.4 ± 4.0	7.3 ± 4.8	7.5 ± 3.3	.896
ALC (× 10 ⁹ /L)	0.7 ± 0.5	0.7 ± 0.4	0.6 ± 0.6	.889
High-dose parenteral TMP-SMX				
Time of initiation (days postadmission)	2.8 ± 2.2	2.3 ± 1.9	3.3 ± 2.5	.334
TMP daily dose/BW (mg/kg/d)	10.7 ± 4.3	10.9 ± 3.4	10.5 ± 5.1	.830
Patient outcomes				
Respiratory failure requiring MV (%)	70.0	40.0	100.0	.011*
Graft failure requiring RRT (%)	65.0	30.0	100.0	.003*

Values are expressed as means ± SD or percentage unless otherwise listed.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II; BW, body weight; eGFR, estimated glomerular filtration rate; MV, mechanical ventilation; *PJP*, *Pneumocystis jiroveci* pneumonia; RRT, renal replacement therapy; TMP-SMX, trimethoprim-sulfamethoxazole

* $P < .05$.

(15%). Meanwhile, *Candida spp.* was isolated in 6 patients. There were no differences in acute rejection history, *cytomegalovirus* infection history, and polyomavirus infection history between live and dead patients.

Furthermore, we compared the disease severity between live and dead patients. Our data show that there were no differences between these 2 groups of patients, including APACHE II score on admission day, bacteremia rate, concomitant urinary tract infection rate, serum albumin, creatinine, eGFR, absolute neutrophil count, and absolute lymphocyte count (except for the percentage of inotropic agent use [live vs dead patients, 10% vs 100%]; $P < .001$).

Immunosuppressant regimens before *Pneumocystis jiroveci* hospitalization

Table 2 shows the regimens of the immunosuppressant agents. Compared to *PJP* survivors, deceased patients had a significantly higher daily

dosage of corticosteroids and had a higher serum trough level of tacrolimus before *PJP* hospitalization, which was related to their shorter posttransplant vintage. The mean onset of *PJP* of the deceased patients (1.8 years posttransplant) was shorter than that of the survivors (3.6 years posttransplant); but this did not achieve the statistical significance).

Immunosuppressant dosage reduction after *Pneumocystis jiroveci* hospitalization

We compared the immunosuppressant dosage reduction between patients that lived and those that died. As shown in Table 2, timing of immunosuppressant dosage reduction of the survivors was significantly earlier than that of the deceased. Fifty percent of the survivors' immunosuppressive agents had been reduced on the first day of hospitalization, but none of those who died did ($P = .033$). Meanwhile, the timing of dosage reduction of the first immunosuppressant of the survivors (1.4 days

Table 2. Regimens and Dosage Reduction of the Immunosuppressive Agents

	All	Living	Dead	P Value
Patient number	20	10	10	
Onset of <i>PJP</i> (years posttransplant)	2.7 ± 2.2	3.6 ± 2.6	1.8 ± 1.2	.064
Acute rejection history (%)	45.0	50.0	40.0	1.000
<i>Cytomegalovirus</i> infection history (%)	25.0	20.0	30.0	1.000
<i>Polyomavirus</i> infection history (%)	35.0	40.0	30.0	1.000
IS regimens before admission				
Corticosteroids, oral (n; %)	18; 90.0	8; 80.0	10; 100	.474
Daily dosage/BW (mg/kg/d)	0.17 ± 0.12	.09 ± .04	0.23 ± 0.13	.009*
Tacrolimus (n; %)	18; 90.0	9; 90.0	9; 90	1.000
Daily dosage/BW (mg/kg/d)	0.08 ± 0.07	.08 ± .09	0.07 ± 0.04	.790
Serum concentration (trough) (nmol/L)	7.6 ± 3.7	5.3 ± 1.7	9.8 ± 3.7	.004*
Cyclosporine (n; %)	2; 10.0	1; 10.0	1; 1.0	1.000
Daily dosage/BW (mg/kg/d)	3.66	2.77	4.55	NA
Serum concentration (C2) (nmol/L)	669.8	490.5	849.5	NA
Mycophenolate mofetil (n; %)	18; 90	9; 90	9; 90	1.000
Daily dosage/BW (mg/kg/d)	19.87 ± 7.05	16.71 ± 6.42	23.03 ± 6.48	.054
Sirolimus (n; %)	6; 30	3; 30	3; 30	1.000
Daily dosage/BW (mg/kg/d)	0.04 ± 0.01	.05 ± .01	0.03 ± 0.01	.232
Serum concentration (trough) (nmol/L)	8.3 ± 2.8	7.2 ± 3.3	10.1 ± 1.0	.342
IS dosage reduction after admission				
IS dosage reduction (%)	95.0	90.0	10.0	1.000
Kinds of IS drugs being reduced	1.5 ± 0.6	1.4 ± 0.7	1.6 ± .5	.476
IS dosage reduction on the admission day (%)	25.0	50.0	.0	.033*
Time of the 1st IS reduction (days postadmission)	3.4 ± 3.1	1.4 ± 2.0	5.1 ± 2.8	.005*
Reduced percentage of the 1st IS drug	68.9 ± 28.7	71.5 ± 28.9	66.5 ± 29.8	.716
Time of the 2nd IS reduction (days postadmission)	6.4 ± 6.5	4.0 ± 8.4	8.1 ± 4.7	.299
Reduced percentage of the 2nd IS drug	46.5 ± 21.0	41.3 ± 14.5	5.2 ± 25.1	.496

Values are expressed as mean ± SD or percent unless otherwise listed.

Abbreviations: BW, body weight; IS, immunosuppressants; NA, not applicable; *PJP*, *Pneumocystis jiroveci* pneumonia.

* $P < .05$.

postadmission) was significantly earlier than those that died (5.1 days postadmission; $P = .005$).

Determinants of *Pneumocystis jiroveci* mortality

As shown in Table 3, logistic regression analysis indicated that for each 1 day late in reducing the immunosuppressive agents, there was a 1.966-fold risk of increase in *PJP* mortality ($P = .023$). In addition, not only the timing, but also the quantity, of immunosuppressant reduction matters. If either one of the immunosuppressive agent's dosage was reduced more than 50% within 2 days of hospitalization, there was a 92.6% risk reduction in *PJP* mortality ($P = .035$).

Clinical outcomes

Unfortunately, 10 of the 20 *PJP* patients died. Our *PJP* patients presented with a high mortality rate (50%) and had a poor prognosis despite aggressive therapies, as evidenced by the rapid initiation of high-dose parenteral TMP-SMX (average initiation time: 2.8 days postadmission). All deceased patients developed respiratory failure that required mechanical ventilation, and all of them developed graft failure that required renal replacement therapy. In contrast, *PJP* survivors had a

Table 3. The Effect of Aggressive Immunosuppressant Reduction on *PJP* Mortality

Factor	OR	95% CI		P Value
		Lower	Upper	
Time of the 1st IS reduction (days postadmission)	1.966	1.099	3.515	.023*
Either one of IS reduction > 50% within 2 days after admission (reference: no)	0.074	0.007	0.835	.035*

Abbreviations: CI, confidence interval; IS, immunosuppressants; OR, odds ratio; *PJP*, *Pneumocystis jiroveci* pneumonia

* $P < .05$.

significantly lower proportion of intubation requirement (40%; $P = .011$) and requirement for renal replacement therapy (30%; $P = .003$).

Table 4 summarizes the long-term outcomes of the *PJP* survivors. We found that all patients were successfully weaned from the mechanical ventilator during the *PJP* hospitalization. Mean duration of dosage reduction of immunosuppressants for more than 50% of the *PJP* survivors was 21.9 ± 4.5 days. Two survivors began to depend on dialysis therapy before discharge. Graft loss occurred in 2 other patients 2.6 and 11.7 months after discharge. The former patient encountered a fatal arrhythmia during hemodialysis therapy 5.8 months after discharge and died. There were no episodes of

suspicious clinical acute rejection or allograft necrosis occurred during a mean follow-up of 2 years.

Table 4. Long-Term Outcomes of *PJP* Survivors (n=10) After Discharge

	Patient Number (n)	Percentage (%)	Follow-Up (mo)
All patients	10	100.0	25.3 (3.2-60.6)
Graft kidney necrosis	0	0.0	
Acute rejection	0	0.0	
Dialysis therapy dependence			
Graft loss owing to <i>PJP</i>	2	20.0	
Graft loss afterwards	2	20.0	7.2 (2.6-11.7)
Mechanical ventilator dependence	0	0.0	
Mortality afterwards	1	10.0	5.8*

Values are expressed as means (range).

Abbreviation: *PJP*, *Pneumocystis jirovecii* pneumonia

*Cause of death: fatal arrhythmia during hemodialysis

Discussion

The findings of this study indicate that disease severity is equivalent between those patients that lived and those that died. Aggressive dosage reduction of immunosuppressive agents is beneficial for *PJP* recovery in RTRs. Furthermore, we did not identify any clinically suspected rejection episodes or any allograft necrosis in the survivors, whose immunosuppressant had been reduced much more drastically. We suggest that prompt and sufficient dosage reduction of immunosuppressants is life-saving in such circumstance and does not increase the risk of long-term acute rejection.

The concern of immunosuppressant dosage reduction in RTRs is mostly related to the fear of future allograft rejection or necrosis. Sileri and associates have proposed a standardized protocol for treating severe pneumonia in RTRs. In their protocol, the calcineurin inhibitors were withheld for the first 2 or 3 days. There were no acute rejection episodes during hospitalization,⁷ which is in accordance with our *PJP* survivors' outcomes. In our study, we did not identify any clinically evident acute rejection in the *PJP* survivors, whose immunosuppressive agents had been significantly reduced for an average duration of 3 weeks. We further followed-up our patients for a mean duration of 2 years, and no acute allograft rejection or necrosis was documented.

The majority of studies has reported the *PJP* occurs 3 to 6 months after renal transplant.^{1, 4, 14-18} In our study, the average time of *PJP* onset was 2.7 years after renal transplant. The late onset of our *PJP* cases may be due to the routine first 6-month *PJP* chemoprophylaxis in our institute. The incidence of

PJP is 1.7% in our RTRs, probably because we did not routinely give *PJP* chemoprophylaxis after episodes of allograft rejection. Nevertheless, a large scale study has shown that prior acute rejection is not associated with development of *PJP* disease.⁵ On the other hand, our data show that a prior acute rejection history, low eGFR, and lymphocytopenia are not determinants of *PJP* mortality.

In our study, the daily dosage of corticosteroids and the serum level of tacrolimus of the dead patients before admission were significantly higher than those who survived. However, the posttransplant duration of the dead patients was shorter. This is because the recommended targets of immunosuppressive drug level were different depending on their posttransplant vintage.¹⁹ However, though the baseline tacrolimus level of the live patients was already lower than that of the dead patients, the immunosuppressive agents of the live patients was tapered more aggressively. Outcome data of the survivors revealed that such aggressive immunosuppressant dosage reduction is life-saving, and its long-term risk of acute allograft rejection is minimal.

Limitations of our study are the small number of *PJP* patients and its retrospective design. However, the incidence of *PJP* in RTRs decreases after the introduction of routine *PJP* chemoprophylaxis. Despite the patient number being limited, we found a significant association between the aggressiveness of immunosuppressant dosage reduction and *PJP* survival.

In conclusion, this study indicates that immunosuppressant dosage reduction should be prompt and sufficient for immunity recovery. In addition, our results suggest that aggressive immunosuppressant dosage reduction possesses a minimal risk of in-hospital and long-term acute rejection.

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