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The incidence of cytomegalovirus infection in renal transplant patients: single-center study

Duangchit Panomvana Na Ayudhaya*
Kearkiat Praditpornsilpa** Karunrat Tewthanom*

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Background and objective : *Cytomegalovirus (CMV) infection is a serious problem in renal transplant patients. The purpose of this study was to determine the incidence of CMV infection in Thai renal transplant recipients.*

Setting and methods : *The data were collected from medical records of patients who had renal transplantation from January 1998 to December 2002 at the Nephrology Unit, King Chulalongkorn Memorial Hospital.*

Design : *Descriptive retrospective analysis.*

Results : *The information of 91 out of 114 renal transplanted patients at the Nephrology Unit were retrieve and analyzed. They were 47 men and 44 women. Their mean age was 41.89 $\pm$ 11.82 years and the mean year of transplantation was 2.51+ 1.53 years. Most patients (46.2 %) had end-stage renal failure from unknown causes, while 13.2 % were diabetes nephropathy, and 14.3 % were chronic glomerulonephritis respectively. More than half (64.8%) of the patients received cadaveric renal transplantation while the rest (35.2 %) received living related donors. Eighty-three of patients (91.2 %) had seropositive CMV antibodies (IgM or IgG) in both donors and recipients (D+/R+). Four patients (4.4 %) had D-/R-; three*

* Department of Clinical Pharmacy (Project), Faculty of Pharmaceutical Sciences, Chulalongkorn University
** Department of Medicine, Faculty of Medicine, Chulalongkorn University

patients (3.3 %) had D-/R+; and only one patient (1.1 %) had D+/R-. Triple immunosuppressive agents were used in all patients at the early post transplantation. Nine of eighty-three (11 %) seropositive patients (D+/R+) got CMV infection. All CMV infections were diagnosed during the first 7 months after transplantation. Among the 91 investigated patients, 31 (34.06 %) patients had their cyclosporine levels higher than the therapeutic ranges while the rests were within targeted ranges. Seven out of ten (70 %) patients who got CMV infection had their cyclosporine concentrations higher than targeted ranges. Therefore the proportion of CMV infections were significantly higher in the group that had cyclosporine higher than therapeutic level as compared to the group that had within the therapeutic level (p=0.011). Antiviral drugs were used for pre-emptive and secondary prophylaxis therapy. Ganciclovir was the main drug used for standard treatment and prophylaxis. Most patients could tolerate the antiviral therapy. Eight patients (80 %) were improved, one patient (10 %) suffered from graft rejection and one patient (10 %) died.

Conclusion : *The incidence of CMV infection was found in 11 % of renal transplant patients. All CMV infected patients were diagnosed during the first seven months post transplantation while their cyclosporine concentrations were mostly higher than targeted ranges. The majority of the transplantation patients showed good clinical response to antiviral drug therapy.*

Keywords : *Cytomegalovirus, Renal transplant.*

Reprint request : Panomvana Na Ayudhaya D, Department of Clinical Pharmacy (Project), Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10400, Thailand.

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ปัญหาและวัตถุประสงค์ : *การติดเชื้อ Cytomegalovirus เป็นปัญหาสำคัญในผู้ป่วยปลูกถ่ายไต การวิจัยครั้งนี้ทำเพื่อหาอุบัติการณ์การติดเชื้อดังกล่าวในผู้ป่วยคนไทยที่ปลูกถ่ายไต โดยศึกษาช่วงเวลาที่พบอุบัติการณ์การติดเชื้อบ่อยหลังการปลูกถ่ายไต ศึกษาความสัมพันธ์ระหว่างระดับยากดภูมิคุ้มกันในเลือดกับอุบัติการณ์การเกิดการติดเชื้อรวมถึงการศึกษาผลของการใช้ยาต้านไวรัสในกลุ่มประชากรดังกล่าว*

สถานที่ทำการวิจัยและวิธีการวิจัย : *ทำการเก็บข้อมูลจากแบบบันทึกประวัติผู้ป่วยที่มาทำการปลูกถ่ายไตระหว่างเดือนมกราคม 2541 ถึง เดือนธันวาคม 2545 ที่หน่วยโรคไต โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย : *เป็นการวิเคราะห์ข้อมูลเชิงบรรยายแบบย้อนหลัง*

ผลการศึกษา : *ข้อมูลและการวิเคราะห์ผลผู้ป่วยจำนวน 91 ราย จากผู้ป่วยที่มาปลูกถ่ายไตในช่วงเวลาที่ทำการศึกษาจำนวนทั้งหมด 114 ราย เป็นเพศชาย 47 ราย เพศหญิง 44 ราย อายุเฉลี่ยเท่ากับ 41.89±11.82 ปี มีระยะเวลาการปลูกถ่ายไตเฉลี่ย 2.51± 1.53 ปี ผู้ป่วยส่วนใหญ่ (46.2 %) มีภาวะไตวายโดยไม่ทราบสาเหตุ 13.2 % มีสาเหตุมาจากไตเสื่อมเพราะโรคเบาหวาน และ 14.3 % มีภาวะกรวยไตอักเสบเรื้อรัง ผู้ป่วยมากกว่าครึ่ง (64.8 %) ได้รับไตจากผู้บริจาคที่เสียชีวิต ร้อยละ 35.2 ได้รับบริจาคโดยญาติที่ยังมีชีวิต ผู้ป่วย 83 คน (91.2 %) มี seropositive CMV antibody (IgM) ทั้งผู้บริจาคและผู้รับ (D+/R+) ผู้ป่วย 4 ราย (4.4%) มี serology แบบ D-/R- ผู้ป่วย 3 ราย (3.3 %) มี serology แบบ D-/R+ และมีผู้ป่วย 1 รายที่ผู้บริจาคมี seropositive CMV antibody แต่ผู้รับไม่มี (D+/R-) ผู้ป่วยทุกรายได้ยากดภูมิคุ้มกันร่วมกัน 3 ชนิด ในช่วงหลังปลูกถ่ายไตช่วงแรกพบการเกิดการปฏิเสธไตเฉียบพลันในผู้ป่วย 7 ราย (7.7 %)*

และมีผู้ป่วยเสียชีวิต 2 ราย (2.2 %) ผู้ป่วยที่ได้รับการวินิจฉัยว่าติดเชื้อ CMV มีจำนวน 10 ราย (11 %) เป็นชาย 5 ราย หญิง 5 ราย ในจำนวนผู้ป่วยที่มี positive CMV serology (D+/R+) จำนวน 83 ราย ติดเชื้อ CMV 9 ราย (11 %) และผู้ป่วยที่มี negative CMV serology (D+/R-) เกิดการติดเชื้อ CMV (คิดเป็น 100 %) ผู้ป่วยทุกรายตรวจพบการติดเชื้อ CMV ในช่วง 7 เดือนแรกของการปลูกถ่ายไต ผู้ป่วย 31 ราย จาก 91 ราย มีระดับยา cyclosporine ในเลือดสูงกว่าค่าที่กำหนด ผู้ป่วยติดเชื้อ CMV 7 ใน 10 ราย (70 %) มีระดับยา cyclosporine สูงกว่าช่วงการรักษา ดังนั้นทำให้สัดส่วนของผู้ป่วยที่ติดเชื้อ CMV ที่มีระดับยา cyclosporine สูงกว่าช่วงการรักษา มากกว่าผู้ที่ไม่ติดเชื้อที่มีระดับยาอยู่ในช่วงการรักษา (p=.011) การใช้ยาต้านไวรัสจะใช้เป็น pre-emptive และ secondary prophylaxis ยาที่มักใช้เป็นมาตรฐานในการรักษาและป้องกันคือ ganciclovir ผู้ป่วยส่วนใหญ่สามารถทนต่อยาได้ดี ผู้ป่วย 8 คน (80 %) จะมีอาการดีขึ้น ผู้ป่วย 1 ราย (10 %) เกิดภาวะปฏิเสธไต และมีผู้ป่วย 1 ราย (10 %) เสียชีวิต

สรุป : *อุบัติการณ์ของการติดเชื้อ CMV ในผู้ป่วยปลูกถ่ายไตเท่ากับร้อยละ 11 ผู้ป่วยที่ติดเชื้อ CMV ทุกคนจะเกิดการติดเชื้อในช่วง 7 เดือนแรกหลังจากปลูกถ่ายไต และส่วนใหญ่จะมีระดับยา cyclosporine ในเลือดสูงกว่าระดับที่ให้การรักษา ผู้ป่วยส่วนใหญ่มีการตอบสนองทางคลินิกที่ดีต่อการได้รับยาต้านไวรัส*

คำสำคัญ : *Cytomegalovirus, การปลูกถ่ายไต*

Patients with a suppressed immune system, such as renal transplantation suffer from cytomegalovirus (CMV) infection. Thirty percent of kidney transplantation who got CMV infection have fever, 25 % have leukopenia, 20 % have graft failure, and 25 % have mortality. The incidence and severity of symptomatic CMV infections in transplant recipients are related to the intensity of immunosuppression required to prevent graft rejection.[1-6]

Objective

The purpose of the study were :

1. To determine the incidence of cytomegalovirus in Thai renal transplant patient

2. To determine the factors that influence the incidence of cytomegalovirus infection in Thai renal transplanted patients;

3. To explore the out-come of anticytomegaloviral drug therapy and/or prophylaxis in renal transplant patients.

Methodology

I. Population

This descriptive study was performed in renal transplant patients who visited the Nephrology Unit, King Chulalongkorn Memorial Hospital from January 1998 to December 2002. Their data were retrieved from patient medical records.

Inclusion criteria

Male or female patients, older than 18 years, who were admitted in the Nephrology Unit for renal transplantation during the study period were included in this study.

Exclusion criteria

Patients whose data from the medical records were not complete.

II. Data collection

The case record forms were created, namely :

1. Demographic data.

2. Immunosuppressive regimens, adverse drug reaction, and adverse events,

3 CMV disease,

4. Current antiviral medications,

5. Other concurrent medication,

6. Biopsy – proven allograft rejection, graft loss or death.

III. Data analysis

Descriptive statistics were used data analysis and reported in percentage. Chi-square test was used to compare the proportion.

Results

I. Population

There were 114 renal transplant patients who visited the Nephrology Unit from January 1998 to December 2002. There were 91 patients whose data were completed. The demographic data of the patients are presented in Table 1. Most patients (94.6 %) received triple immunosuppressive regimens as shown in Figure 1. During 1998-2002, the triple regimens of Cyclosporine, prednisolone and azathioprine were mostly used as shown in Figure 2. Combined data including sign and symptoms, viral culture, CMV antibodies titer and PCR technique were used for the detection and diagnostic of CMV infection and CMV diseases. The result was shown in Table 2. Nine of eighty- three (11%) of seropositive patients (D+/R+) got CMV infection while the only one patient (100%) who was seronegative recipient (D+/R-) got

CMV infection. The percentage of antiviral used is shown in Table 3. Most patients (9 out of 10) were well tolerated to antiviral. One patient had neutropenia during the administration of ganciclovir. However, she could tolerale ganciclovir after a pause of one week. The concurrent drug administration, adverse events and out comes (graft rejection, compliance and living status) are presented in Table 4, 5, respectively.

Table 1. Demographic data of renal transplant recipients.

Characteristics	Results, n (%)
Recipient (n)	114
Incompleted data (%)	23 (20.2%)
Completed data (%)	91 (79.8%)
Mean age (yr)	41.89 ± 11.82
Gender (n)	91
Male (%)	47 (51.6%)
Female (%)	44 (48.4%)
Number of transplantation (n)	114
1 (%)	112 (98.2%)
2 (%)	2 (1.8%)
Mean transplantation duration (yr)	2.5 ± 1.53
Primary cause of ESRD (n)	91
Unknown (%)	42 (46.2%)
DM nephropathy (%)	12 (13.2%)
Chronic glomerulonephritis	13 (14.3%)
Others (%)	26 (26.3%)
Underlying diseases (n)	91
Hypertension (%)	37 (40.6%)
No underlying (%)	27 (29.7%)
Type of donor graft (n)	91
Cadaveric (%)	59 (64.8%)
Living (%)	32 (35.2%)
CMV Serology (n)	91
D+/R+ (%)	83 (91.2%)
D-/R- (%)	4 (4.4%)
D-/R+ (%)	3 (3.3%)
D+/R- (%)	1 (1.1%)

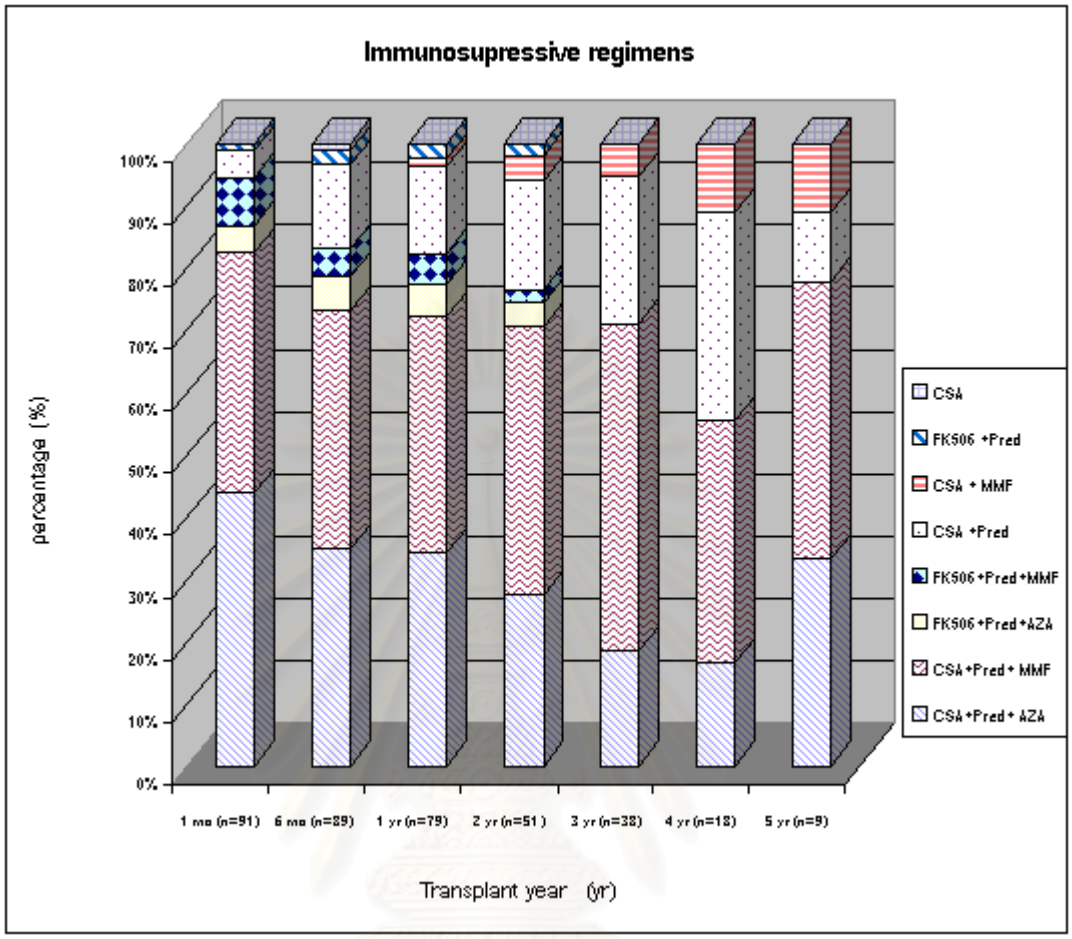

Figure 1. Immunosuppressive regimens.

Table 2. CMV diagnostic results.

Dignosis	N (%)
No CMV disease or CMV infection	81 (89%)
CMV infection	10 (11%)

Table 3. Antiviral drugs.

Antivirals	No (%)
Ganciclovir	4 (40%)
Ganciclovir and Valacyclovir	5 (50%)
Acyclovir	1 (10%)

Table 4. Concurrent drug administration and adverse events.

Characteristics (n=91)	No (%)
Concurrent drugs	
Antilipidemia	65/91 (71.4%)
Antihypertensive	90/91 (98.9%)
Cotrimoxazole	60/91 (65.9%)
Adverse events	
Dyslipidemia	51/91 (56.04%)
Hypophosphatemia	36/91 (39.56%)
Urinary tract infection	23/91 (25.27%)
Upper Respiratory tract infection	8/91 (8.79%)
Gum hyperplasia	8/91 (8.79%)

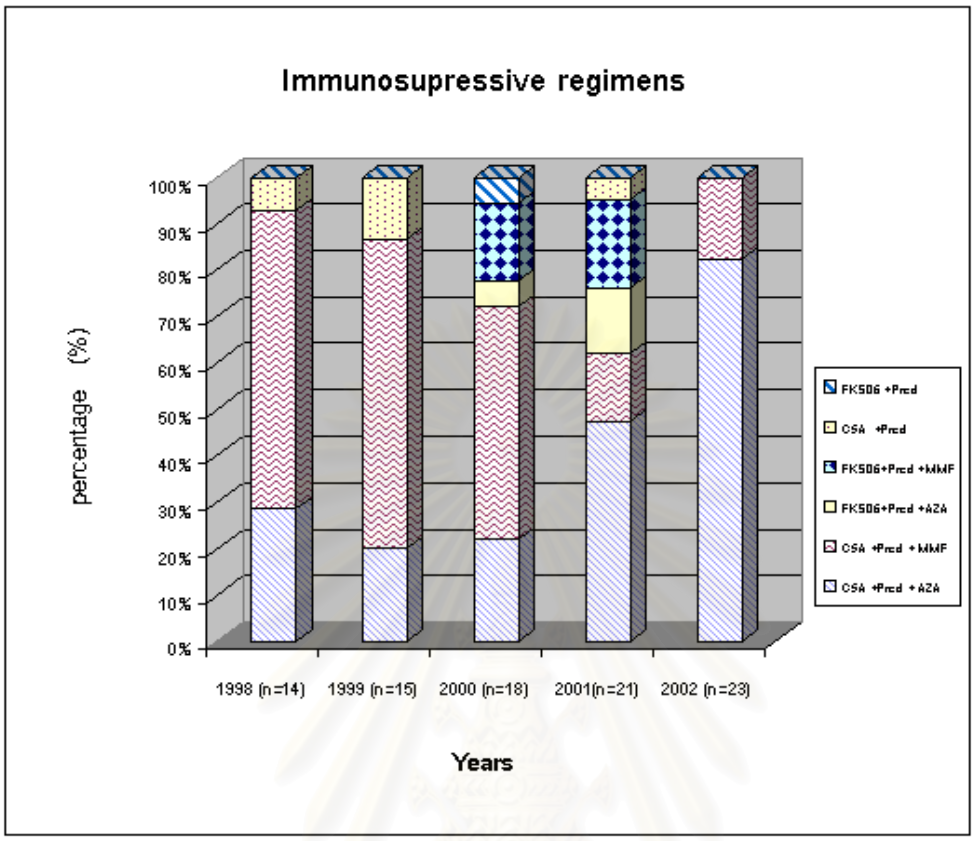

Figure 2. Immunosuppressive regimens 1998 - 2002.

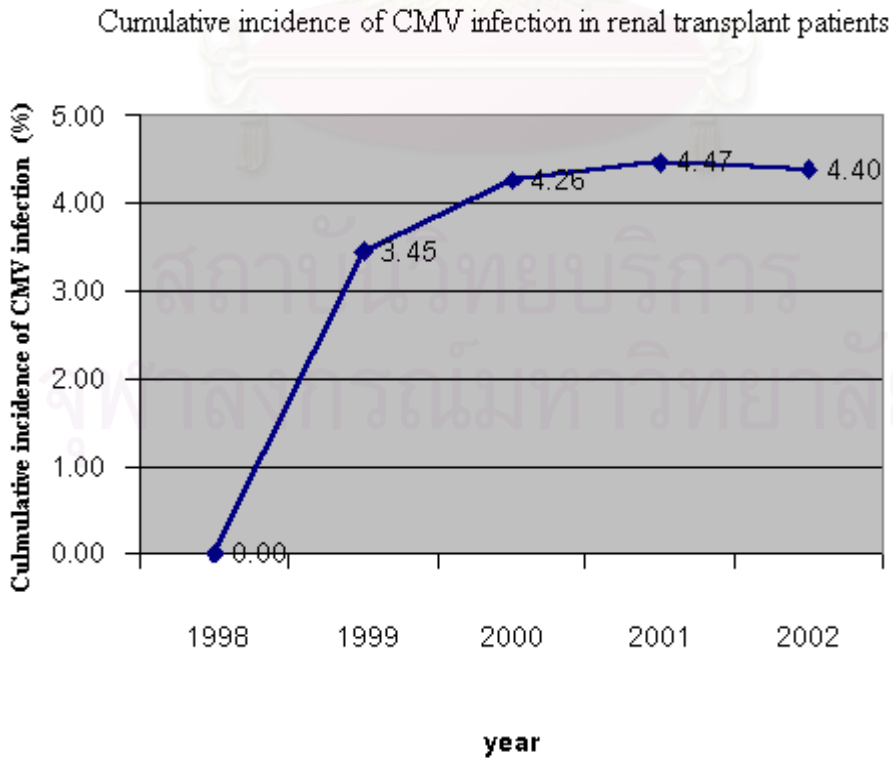

Figure 3. The incidence of CMV infection in renal transplant patients in each years.

Table 5. The outcomes (graft rejection, compliance living status) in renal transplant patients.

Characteristics	No (%)
Graft rejection (n=91)	
No rejection	84 (92.3%)
Rejection	7 (7.7%)
Compliance	
Good compliance	83 (91.2%)
Non-compliance	8 (8.8%)
Status	
Death	2 (2.2%)
Active (alive)	89 (97.8%)

II. The incidence of CMV infection

The incidence of CMV infection was 11%. The cumulative incidence of each year is shown in Figure 3. The average incidence was 3.3 events per 100 person years.

III. Focus on CMV infected patients

The characteristics of renal transplant with CMV infected patients were presented in Table 6.

Among the 90 patients who used cyclosporine, seven patients had CMV infection. Chi square test indicated that the proportion of CMV infection was significantly higher in the high cyclosporine concentration group as compared to the within targeted range group (p=0.0011) as shown in Table 7. The odd ratio of proportion of CMV infected patients and non-CMV patients who ever had high cyclosporine concentration was calculated as shown in Table 8. The t-test of mean cyclosporine concentrations were calculated at Table 9 and Table 10 for comparison of drug concentrations either between first 6 months and last 6 months or between CMV infected and non-CMV infected patients, respectively. Both results were shown significantly statistical differences of mean cyclosporine concentrations of 2 groups ($p<0.001$).

Table 6. Characteristics of renal transplant with CMV infected patients.

Characteristics	No (%)
Age (yr)	Mean $\pm$ SD = 36 $\pm$ 14.26
Transplant duration (yr)	Mean $\pm$ SD = 1.63 $\pm$ 1.29
Gender	10
Male	5 (50%)
Female	5 (50%)
Donor /Reciepients CMV status	10
D+/R+	9 (90%)
D+/R-	1 (10%)
Type of donor	10
Cadaveric	8 (10%)
Living	2 (20%)

Table 6. Continuous.

Characteristics	No (%)
Time diagnosis	10
1 month postransplant	3 (30%)
2 months postransplant	1 (10%)
4 months postransplant	3 (30%)
5 months postransplant	2 (20%)
7 months postransplant	1 (10%)
Immunosupressive plasma concentration	10
High concentration	7 (70%)
Within therapeutic range	3 (30%)
MMF used	10
Not received	7 (70%)
Received	3 (30%)
Type of therapy	10
Combination (pre-emptive and prophylaxis)	9 (90%)
Treatment of establish disease	1 (10%)
Anitivirals	10
Ganciclovir	4 (40%)
Ganciclovir and Valacyclovir	5 (50%)
Acyclovir	1 (10%)
Adverse drug reaction (ADR)	10
No ADR	9 (90%)
ADR	1 (10%) test
Out come	10
Improved	8 (80%)
Rejection	1 (10%)
Death	1 (10%)

Table 7. The proportion of CMV infection between patients who had high cyclosporine level and within targeted ranges and Chi square test..

Characters	High cyclosporine concentration	Within targeted ranges	Total
CMV infection	7	3	10
No CMV infection	24	57	81
Total	31	60	91
X^2 test	X^2 value = 6.459, p value = 0.011		

Table 8. Risk Estimation.

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for cyclosporine concentration (in therapeutic range / higher)	5.542	1.321	23.253
For cohort 1 = No CMV	1.227	1.006	1.497
For cohort 1 = CMV	.221	.061	.797
N of Valid Cases	91		

Table 9. t test of cyclosporine concentration (C_0, C_2 value) between the first 6 months and the last 6 months.

Parameters	At first 6 month	At last 6 month	p-value
(Mean ± SD)C_0 (μg/mL)	297.25± 87.91	227.54± 48.8	p< 0.01
(Mean ± SD)C_2 (μg/mL)	1326.60.± 227.65	1045.33± 157.48	p<0.01

Table 10. t test of cyclosporine concentration (C_0, C_2 value) between CMV infected and non CMV infected renal transplant patients.

Parameters	Non-CMV	CMV	p-value
(Mean ± SD)C_0 (μg/mL)	271.73± 87.01	374.29± 140.97	p< 0.01
(Mean ± SD)C_2 (μg/mL)	1172.81± 227.65	1206.34± 157.48	p<0.01

Discussion

In this retrospective study, this incidence of CMV infection is 11 %. The incidence density is 3.3 events per 100 person years. This number was higher than previous reports in the United States (1.26 events per 100 person years). [2] The associated factors of CMV infection in renal transplanted patients could not be identified due to limited number of the patients. Nevertheless, several interesting points should be remarked; first, donor/recipients CMV status, one patient was classified as “high risk” because he had seropostive donor and negative recipient (D+/R-). He died after one year post transplantation, even though he had ganciclovir for pre-emptive therapy and valacyclovir for secondary prophylaxis. The other nine patients were seropositive both donors and recipients (D+/R+). The retrospective study in the Thai Red Cross Society found that 96 % of cadaveric donors had

seropositive of CMV. [7] Second point is time of infection, most patients were diagnosed as CMV infection during the first six months of post transplantation. It is similar to the time line study of opportunistic infection in renal transplant patients. [1,3,8] From this study, the frequency of CMV infection was high in 1 and 4 months of after the transplantation. Therefore, the prophylaxis duration should be started before one month of post transplantation and continue at least 3-4 months of post transplantation as in some guidelines.[5,9] The third point that should be considered is using of immunosuppressive agents. As previously presented in the results, cyclosporine has been the main immunosuppressive agents since 1998 to 2002. The guideline for C_2 (concentration at 2 hr) monitoring of cyclosporine is currently used.[10,11] The proportion of the patients who had high cyclosporine concentration was significantly higher in CMV infected patients than non CMV infected patients. The cyclosporine concentrations were statistically significant higher in CMV infected groups than the normal renal transplant patients. Therefore, the association between cyclosporine concentration and the incidence of CMV infection may exist.

Gangciclovir has been used as the gold standard of treatment and prophylaxis of CMV infection in renal transplanted patients since it showed positive results from the clinical trials. [12-18] The duration of prophylaxis using oral ganciclovir and valacyclovir was 3 months after 1-2 weeks treatment of ganciclovir according to the international guidelines. [5,9] One patient who developed CMV retinitis, using acyclovir for prophylaxis. Eventhough this agent is not recommended as first line in CMV prophylaxis, the results from RCT showed 74 % of relative risk reduction compared with placebo.[19]

Most patients could tolerate the antiviral regimens. Only one patient had adverse drug reaction from ganciclovir. Eight of the ten infected patients improved. Large scale clinical trial and long-term follow-up are needed to confirm the effectiveness of antiviral therapy in Thai renal transplanted patients.

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