Assessment of Risk Factors and Outcome of Early Versus Late Cytomegalovirus Infection Infection in Living-related D+/R + Renal Allograft Recipients

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Abstract

Introduction: Cytomegalovirus infection (CMV) in a kidney transplant recipient (KTR) is a serious complication resulting in increased morbidity, mortality and reduced graft survival. There is limited data on early (within 3 months posttransplant) CMV infection (ECMVI) vs. late CMV infection (LCMVI) in patients not receiving CMV prophylaxis. In India, majority of kidney transplants are D + R + combination. This study aimed to compare the risk factors and outcome of ECMVI vs. LCMVI in living related post-KTR. **Methods:** This was a single-center ambispective study of adult KTR from living donor between January 2001 and December 2015 who had CMV infection. This study had two cohorts: retrospective and prospective. Retrospective cohort included all KTR from January 2001 to September 2014. Prospective cohort included KTR who received transplants from October 2014 to December 2015. Of both cohorts, patients with early and late CMV infection were included. All patients received triple-drug immunosuppression. CMV infection was diagnosed when KTR had detectable CMV copies > 500/mL. In the prospective cohort, CMV PCR was done at 45 days, 3, 6, 9 and 12 months in all patients. Patients with CMV were treated on conventional lines. All patients were followed up till June 2016. **Results:** Of 2175 retrospective cohort, 97 and of the 155 prospective cohorts 75 had CMV infection, total being 172 CMV infections. Of these, 90 patients had ECNVI and 82 LCMVI. Induction was used in 48.8% in ECMVI group vs. 35.3% in LCMVI group (p = 0.02). CNI toxicity was present prior to CMV infection in 15 (17.4%) in ECMVI as compared to 14 (17.9%) in LCMVI (P = 0.93). In the ECMVI, 6 (6.6%) had acute rejection as compared to 13 (15.8%) in the LCMVI (P = 0.05). While asymptomatic CMV infection was more common in early (63.3% vs 37.8%, P = 0.001), symptomatic CMV without tissue diagnosis was more common in late (54.8% vs. 31.1%, P = 0.002). Total duration of post-transplant follow-up was 22.8 ± 22.1 months in ECMVI as compared to 49.7 + 40.9 months in the LCMVI (P < 0.001). The serum creatinine at last follow-up was 1.9 ± 1.6 mg/dL in ECMVI group and 2.4 ± 2.0 mg/dL in LCMVI (P = 0.02). **Conclusion:** In D+/R + living renal transplant recipients, without routine CMV prophylaxis, late CMV infection had more tissue invasive disease and is associated with inferior graft function on long-term follow-up.

Keywords: *CMV infection, D+/R+, early and late CMV, kidney transplant*

Introduction

Cytomegalovirus (CMV) infection in a kidney transplant recipient (KTR) is a serious complication resulting in increased morbidity, mortality and reduced graft survival.[1] Its incidence in KTR is around 20–60%.[2] The risk of CMV infection is maximum in kidney transplant among CMV seropositive donor/CMV seronegative recipient (D+/R–) as compared to kidney transplants among D–/R–.[3,4] The risk is moderate in D+/R + and D–/R+ transplants.[5] The incidence of CMV infection in D+/R+ patients varies from 5 to 30%.[6] In the absence of CMV prophylaxis, infection generally oc`curs before the third month following transplant and is called early CMV infection (ECMVI). Risk factors for ECMVI include high viral load, primary infection (D+R–), use of induction therapy [anti-thymocyte globulin (ATG), muromonab-CD3, and alemtuzumab], high calcineurin inhibitor levels, and prior anti-rejection therapy. However, few studies have addressed impact of combinations of risk factors.[7] CMV infection, even in the absence of CMV disease, can cause graft dysfunction,

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reduced graft survival.[8,9] CMV disease is an independent risk factor for acute rejection within the first 100 days and for patient survival.[10]

Despite significant reductions in the incidence of ECMVI by the use of prophylaxis, 18–31% of KTR still develop CMV disease (CMVD) after the antiviral prophylaxis is discontinued.[11–13] CMV infection in this setting, termed late-CMV infection (LCMVI), is an important clinical problem that is associated with significant morbidity.[14] and is not well studied. The LCMVI is associated with more tissue-invasive infections, especially gastrointestinal CMV disease, compared to ECMVI.[4] LCMVI is also associated with significantly decreased patient and graft survival.

There are limited data on comparison of ECMVI and LCMVI in D+/R+ recipients, more so when CMV prophylaxis is not being used. The incidence of ECMVI and CMVD in D+/R+ recipients was 70% and 20%, respectively, in one study due to higher degree of immunosuppression during early post-transplant period.[15] In a study by Murray *et al.*, after cessation of prophylaxis at 3 months, 47% of D+/R + recipients develop CMV viremia, of which 19.5% developed symptoms.[16] In India, majority of kidney transplants are D + R + combination. This study aimed to compare the risk factors and outcome of early vs. late CMV infection in living post-KTR.

Material and Methods

Study design

This was a single-center ambispective study conducted in the Departments of Nephrology and Microbiology at our institute. The study included patients who underwent renal transplants between January 2001 and December 2015 and had CMV infection. All pediatric patients and deceased donor transplant were excluded from the study.

Methodology

This study had two different cohorts: retrospective and prospective cohort. Retrospective cohort included all KTR who underwent living renal transplantation (LRT) from January 2001 to September 2014 and had CMV infection/disease. Prospective cohort included patients who received LRT from October 2014 to December 2015. Of both cohorts, patients with early and late CMV infection were included. All patients received triple-drug immunosuppression which included steroid, calcineurin inhibitor (Tacrolimus or Cyclosporine) and an antiproliferative agent (Mycophenolate mofetil or Azathioprine). Patients who required induction therapy received either Basiliximab or antithymocyteglobulin (ATG).

Early CMV infection was diagnosed when KTR had detectable CMV copies >500/mL by PCR technique within 3 months of transplant, whether detected on routine screening or detected once patients had features suggestive of CMV infections. Late CMV infection was diagnosed when KTR had CMV infection after 3 months of transplant, again whether detected on routine screening or detected once patients had features suggestive of CMV infections. CMV disease was defined by evidence of CMV infection with organ involvement attributable to CMV infection. CMV prophylaxis was given only if patient received ATG induction.

In the retrospective cohort, record of patients who developed CMV infection were looked in for clinical features, investigations, CNI level at the onset of CMV infection, CMV-DNA PCR at diagnosis of CMV and post-treatment, duration of antiviral therapy, presence of graft dysfunction and opportunistic infections during CMV infection from our departmental renal transplant registry maintained since 1991. Patient's data were analyzed for presence of risk factors. Patients renal functions at last follow-up visit were recorded.

In the prospective cohort, Quantitative CMV-PCR testing (By Qiagen Kit) was done at 45 days, 3, 6, 9 and 12 months in all patients. Patients who had CMV-PCR >500 copies/mL were treated with oral valganciclovir for 21 days followed by 3 months of secondary prophylaxis. Repeat CMV-PCR levels were done after completion of therapy to look for viral clearance. Patient's hemogram, kidney function test, CNI levels were done at initiation of treatment and after 21 days. All patients with clinical suspicion of CMV infection also underwent CMV-PCR levels other than the above scheduled days. All patients were followed up till June 2016.

Institutional Ethics Committee approval was taken for the study. Written and informed consent was sought from all patients enrolled in the study in prospective cohort.

Data analysis

Data were analyzed by Stata 11.2 and presented in mean (SD), median, (min, max) and frequency (percentage). Categorical variables were compared in two groups by using Chi-square/Fisher exact test (as applicable). Continuous variables were compared in two groups by independent t test (following normal distribution/Wilcoxon rank sum test (for skewed data) as applicable. Univariate and multivariable logistic regression by inter method (variable whose P value less than 0.25 was considered in multiple logistic regression) was applied to assess risk factors for CMV infection and unadjusted and adjusted Odds ratio were calculated. A value of $P < 0.05$ was considered as statistically significant.

Results

Of 2175 retrospective cohort, 97 and of the 155 prospective cohorts 75 had CMV infection [Table 1]. Combining both the cohorts, of the total 172 CMV infections, 90 (52.3%) patients had early CMV infection and 82 (47.7%) had

late CMV infection. All the patients in the study had D+/R + CMV status. Baseline demography of patients with early and late CMV infection are shown in Table 2. Total number of rejections in ECMVI and LCMVI were 6 and 13, respectively, of which 4 and 9 patients in ECMVI and LCMVI, respectively, had acute rejection prior to onset of CMV infection. Total duration of post-transplant follow-up was 22.8 ± 22.1 months in early CMV group as compared to 49.7 + 40.9 months in the late CMV group ($P < 0.001$) [Table 2].

Table 1: Contribution of number of patients of early and late CMV infection from two cohorts of the study

	Early CMV	Late CMV	Total
Retrospective cohort	37	60	97
Prospective cohort	53	22	75
Total	90	82	172

Details of assessment of risk factor for early and late CMV are shown in Table 3. In the early CMV infection group, 6 (6.6%) patients had acute rejection as compared to 13 (15.8%) in the late CMV group ($P = 0.05$). However, acute rejection prior to onset of CMV infection was seen in 4 (4.4%) patients in the early CMV group and 9 (10.9%) patients in the late CMV group ($P = 0.15$). CNI toxicity were present prior to onset of CMV infection in 15 (17.4%) in ECMVI group as compared to 14 (17.9%) in LCMVI group ($P = 0.93$). The clinical features of the patients with ECMVI and LCMVI groups are shown in Table 4. Outcome was assessed by comparing episodes of acute rejection post CMV infection, serum creatinine at last follow-up, and graft and patient survival [Table 5]. The serum creatinine at last follow-up was 1.9 ± 1.6 mg/dL in ECMVI group and 2.4 ± 2.0 mg/dL in LCMVI group which was statistically significant ($P = 0.02$).

Table 2: Baseline characteristics of patients with Early and Late CMV infection in Combined Cohort

Baseline variables	Early (*n*=90)	Late (*n*=82)	*P* 95% CI
Age (years)	32.8±10.2 (30.8-34.9)	35.2±11.2 (32.7-37.8)	0.12 CI -2.4, -5.6-0.81
Sex Male (%)	77 (85.5)	67 (81.7)	0.49
Basic disease no (%)			0.90
CGN	0	0	
CTID	5 (5.6)	4 (4.8)	
DN	5 (5.6)	4 (4.8)	
PKD	1 (1.1)	1 (1.2)	
Unclassified	79 (87.7)	83 (89.0)	
HCV infection Prevalence (%)	10 (11.2)	5 (6.1)	0.28
Dialysis Vintage (months), median (p25-p75)	8 (5-12)	8 (5-13)	0.83
Blood Group, *n* (%)			0.18
A	18 (20)	15 (18.2)	
B	35 (38.8)	34 (41.4)	
O	23 (25.5)	28 (34.1)	
AB	14 (15.5)	5 (6.0)	
Donor Age (years)	46.4±10.2	44.6±11.2	0.26 CI 2.07, -1.1-5.3
Donor Sex Female, *n* (%)	73 (81.1)	56 (70.0)	0.09
HLA mismatch (of 6)	3.6±1.2	3.1±1.4	0.11
Induction	44 (48.8)	29 (35.3)	0.02
Basiliximab	40 (90.0)	21 (72.4)	0.006
Daclizumab	0	3 (10.3)	0.0018
ATG	4 (9.0)	5 (17.3)	0.62
DGF	1 (1.1)	0	0.30
S. Cr. immediate post RT (mg/dL)	1.3±0.4	1.3±0.4	0.56
CMV status D+/R+	90 (100)	82 (100)	
CMV prophylaxis, *n* (%)	4 (4.4)	6 (7.3)	0.5
Acute Rejection	6 (6.6)	13 (15.8)	0.05
Acute Rejection prior to CMV infection	4 (4.4)	9 (10.9)	0.15
Total follow-up Post -RT (months)	22.8±21.0	49.7±40.9	< 0.001

CGN-Chronic Glomerulonephritis, CTID- Chronic Tubulointerstitial Nephritis, DN- Diabetic nephropathy, PKD- Polycystic Kidney Disease, DGF- Delayed Graft Function, RT-Renal transplant, ATG-Antithymocyte Globulin, CMV- Cytomegalovirus

Table 3: Risk factors for Early vs. Late CMV infection

Risk Factors	Early (*n*=90)	Late (*n*=82)	*P* 95% CI
Recipient's Age (years)	35.1±10.8	32.6±10.4	0.12-2.4, -5.6-0.81
Dialysis Vintage (months), Median (p25-p75)	8 (5-12)	8 (5-13)	0.83
HCV infection	10 (11.1)	5 (6.1)	0.28
Induction	44 (48.8)	28 (35.3)	0.02
Basiliximab	40 (90)	20 (71.4)	0.006
Daclizumab	0	3 (3.8)	0.0018
ATG	4 (9.0)	5 (17.8)	0.62
DGF	1 (1.1)	0	
Acute Rejection prior to CMV infection	4 (4.4)	9 (10.9)	0.15
CNI toxicity episodes prior to CMV infection	15 (17.4)	14 (17.9)	0.93

DGF - Delayed Graft Function, ATG - Antithymocyte Globulin, CMV - Cytomegalovirus

Table 4: Clinical Features of Patients with Early and Late CMV infection

Parameters	Early (*n*=90)	Late (*n*=82)	*P*
Time to onset of CMV infection (days), median (p25-p75)	61 (45-90)	251 (146-365)	0.0002
Clinical Presentation			
I. Asymptomatic	57 (63.3)	31 (37.8)	0.001
II. CMV Symptoms+Tissue diagnosis	2 (2.2)	3 (3.6)	0.57
III. CMV Symptoms+No tissue diagnosis	28 (31.1)	45 (54.8)	0.002
Incidental CMV detection	3 (3.3)	3 (3.6)	0.90
CMV retinitis	0	3 (6.1)	0.11
CNI toxicity prior to CMV infection	15 (17.4)	14 (17.9)	0.93
CMV DNA viral load (copies/ml), median (p25-p75)	9840 (3000-61147)	3500 (1185-11100)	0.01
Other Infections at the time of CMV	19 (21.1)	21 (25.6)	0.82
1	17	21	
2	02	0	
Relapse	3 (3.3)	5 (6.1)	0.48

CNI- Calcineurin inhibitor, CMV- Cytomegalovirus

Table 5: Outcome in Early vs Late CMV infection

Outcome variables	Early (*n*=90)	Late (*n*=82)	*P*
Duration of follow-up	22.8±22.1	49.7±40.9	< 0.001
Mean S. Cr. Just prior to onset/detection of CMV	1.3±0.4	1.6±0.6	0.06
Mean S. Cr. at last follow-up (mg/dL)	1.9±1.6	2.4±2.0	0.02
Graft dysfunction	4 (4.4)	8 (9.7)	0.17
Graft loss	2 (2.2)	5 (6.1)	0.17
No of hospitalization *n*, median (p25-p75)	1 (0-2)	1 (0-1)	0.58
Infectious complications at and after CMV infection	0.8±1.1	0.5±0.8	0.50
Death	7 (7.7)	2 (2.4)	0.32
Cause of death			
Sepsis	6	2	
Road traffic accident	1	0	
Acute rejection (post CMV infection)	2 (2.2)	3 (3.6)	0.15

Discussion

This study was an ambispective study to find out the differences in the risk factors and outcome of ECMVI and LCMVI in D+/R + KTRs, irrespective of their process of inclusion like retrospective cohort and prospective cohort. Most of the studies on CMV infection had predominantly on D+/R- KTRs and also none of them had compared ECMVI and LCMVI in D+/R + patients.

Induction agents

A total of 44 (48.8%) patients in this study received induction in the early CMV infection group and 29 (35.3%)

in the late CMV infection group (P = 0.02). This suggests that induction does affect the time of development of CMV infection in post-transplant period. In majority (75%) of patients, induction used in our study was Basiliximab. Basiliximab use in early and late CMV infection groups was 40 (90%) and 21 (68.9%), respectively (P = 0.006). Impact of ATG could not be studied for significance as number of patients receiving ATG was small, though in the study by San Juan R *et al.*, use of ATG as induction agent was significantly associated with development of early CMV infection (OR 2.1, 95% CI 1.1-3.8,).[17] In another study having 90% KTR with D+/R + status, ATG was associated with risk of ECMVI (73% vs 41%, P = 0.022).[18] However, in a retrospective study by Bhadauria D *et al.* from India, of 521 patients with predominantly LCMVI, median time to CMV was 7.18 ± 4.35 months, 74 (14.2%) patients developed CMV infection, of which 58% received induction.[19] In a metanalysis of 8 trials involving 1871 renal transplant patients by Adu D *et al.*, use of Interleukin 2 antagonist was not associated with significant risk of CMV infection as such (OR, 0.81; 95% CI, 0.62-1.04).[20]

Acute rejection

Acute rejection on one side can be induced by CMV infection because of upregulation of HLA antigen and on other side antirejection treatment can also induce CMV due to increased immunosuppression. In this study, 4 (4.4%) patients in the early CMV group and 9 (10.9%) patients in the late CMV group had acute rejection treatment prior to onset of CMV infection (P = 0.15). In a study by Sagedel S *et al.*, rejection was a significant risk factor for the development of ECMVI in D+/R + patients,[15] whereas in another study by Reusing *et al.*, acute rejection was common in patient who developed LCMVI in D+/R+ patients (24% vs 50%, P < 0.001). Acute rejection was associated with two-fold increase in risk of developing late CMV disease; however, it was not significant.[21] In a study by Browne JB *et al.*, acute rejection preceded in all patients with late CMV infection in D+/R+ group (P < 0.001).[22] Hence, enhanced immunosuppressed state following treatment of acute rejection is a risk factor irrespective of timing of CMV infection.

In our study, there was no significant difference for dialysis vintage, comorbidities like Type 2 Diabetes Mellitus, chronic HCV infection, delayed graft function, and CNI toxicity prior to onset of CMV between the two groups.

In our study, a large number of patients in both the groups were asymptomatic. CMV syndrome was more common in LCMVI group (P = 0.002). CMV retinitis was present only in patients with LCMVI. LCMVI patient also had more common gastrointestinal involvement. In a study of patients with ECMVI, 38.4% and 24.6% had mild and severe disease, respectively.[23] In a study of LCMVI patients from India, common clinical features were diarrhea (38%), transaminitis (27.%), gastritis (17.2%), pneumonia (9.13%) and colitis (4.0%).[19] Further, in another study with LCMVI, of 54 patients, 29 (54%) had viral syndrome and 25 (46%) had tissue invasive gastrointestinal involvement.[21] Therefore, it looks that LCMVI has more tissue invasive disease with predominantly gastrointestinal involvement as compared to ECMVI. It is possible that late CMV infection is detected little late due to infrequent follow-up at that time period of transplant and by then disease has progressed.

Acute rejection as outcome

CMV infection is reported to be a risk factor of acute rejection.[24-26] However, in our study only 5 of 172 (2.9%) patients had acute rejection following CMV infection; 2 (2.2%) in ECMVI and 3 (3.5%) in LCMVI (P = 0.15). As the number of acute rejections itself were less, it was difficult to compare between the two groups. In a study with multiple time-dependent Cox analysis, the relative risk of acute rejection due to CMV infection and CMV disease was 1.6 (1.1–2.5, P = 0.02) and 2.5 (1.2–5.1, P = 0.01), respectively.[25] In another study, of the 46% D+/R + patients, with early CMV antigenemia, there was no effect of CMV infection on acute rejection (29% vs. 17%, P = 0.20).[26] There is no data on risk of acute rejection in LCMVI. In another study by Toupance O *et al.*, of 51 patients with CMV disease, risk of developing acute rejection within one month was significantly high (OR-5.98; 95% CI, 1.21–29.4, P = 0.001). CMV disease had higher risk of inducing acute rejection as against asymptomatic CMV infection.[27] In addition to upregulation of HLA antigen, reduction of immunosuppressants during CMV infection may also be a critical factor for inducing rejection following CMV infection.

Infectious complications post CMV infection

CMV infection predisposes to opportunistic infection. This is due to reduction in CD4 positive cells, increase in CD8 positive cells and disrupted mucosal surfaces by the CMV infection. In this study, in ECMVI group, post-CMV infectious complication was 08 ± 1.1 as compared to 0.5 ± 0.8 in the late CMV group. In the study done by Sagedel *et al.* with a median follow-up of 66.6 months, early CMV infection had no impact on other infections. In a comparison of patients with 70 matched control subjects, CMV disease were found to be independent risk factors for Nocardia infection (odds ratio, 6.9; 95% confidence interval, 1.02–46; P = 0.047) in next 6 months.[28] However, numbers of infectious complications in both early and late CMV infection group were similar in this study (P = 0.50).

Overall outcome

The mean serum creatinine at last follow-up in ECMVI was 1.9 ± 1.6 mg/dL as compared to 2.4 ± 2.0 mg/dL in the late CMV group (P = 0.02). However, prior to onset or detection of CMV infection, serum creatinine in ECMVI

and LCMVI was 1.3 ± 0.4 mg/dL and 1.6 ± 0.6 mg/dL, respectively, which was significantly not different but still after the CMV infection at last follow-up, graft function was inferior in LCMVI than ECMVI, which looks to be impact of CMV infection itself. However, there was no significant difference in graft loss between the two groups. Patients in the LCMVI group had overall a greater number of acute rejections (15.8%) as compared to patients with early CMV infection (6.6%), (P = 0.05) and this might have resulted in higher creatinine at a later stage in late infection group. There are no studies in which ECMVI and LCMVI were compared with graft dysfunction as an outcome. There was lesser number of graft losses in our study in both the groups because a sizeable number of patients had asymptomatic CMV infection and were treated preemptively. Overall, in this study, patients had low acute rejections rate in both the groups. This might also have contributed to better graft function. 7 (7.7%) patients in the early and 2 (2.2%) patients in the late CMV group died during the follow-up period (P = 0.32). The major cause of death in both groups was sepsis. In this study, tissue invasive disease was less in both the groups and that might have contributed to the lower mortality.

Our study has strength that it has a cohesive group of all D+/R + patients with transplant from living donors and without any CMV prophylaxis. However, there is limitation that we had two groups of cohort and approach of defining CMV infection in two groups was different. In retrospective group it was based on symptoms, whereas in prospective group it was based on routine screening for infection. However, as our aim of study was primarily to compare early vs. late CMV infection, we feel it does not matter from which cohort these two sets of patients were included.

Conclusion

In D+/R+ living renal transplant recipients, without routine CMV prophylaxis, late CMV infection had more tissue invasive disease with predominant gastrointestinal involvement and is associated with inferior graft function on long-term follow-up. However, there was no difference in patient and graft survival. Further studies are required for assessing the pattern of CMV infection in D+/R+ KTRs receiving universal prophylaxis.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hodson EM, Jones CA, Webster AC, Strippoli GFM, Barclay PG, Kable K, *et al.* Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: A systematic review of randomised controlled trials. Lancet Lond Engl 2005;365:2105–15.
2. Sia IG, Patel R. New strategies for prevention and therapy of cytomegalovirus infection and disease in solid-organ transplant recipients. Clin Microbiol Rev 2000;13:83–121, table of contents.
3. Crough T, Khanna R. Immunobiology of human cytomegalovirus: From bench to bedside. Clin Microbiol Rev 2009;22:76–98, table of contents.
4. Humar A, Snydman D; AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplant recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 2009;9(Suppl 4):S78-86.
5. Legendre C, Pascual M. Improving outcomes for solid-organ transplant recipients at risk from cytomegalovirus infection: Late-onset disease and indirect consequences. Clin Infect Dis 2008;46:732–40.
6. De Keyzer K, Van Laecke S, Peeters P, Vanholder R. Human cytomegalovirus and kidney transplantation: A clinician's update. Am J Kidney Dis 2011;58:118–26.
7. Kute VB, Vanikar AV, Shah PR, Gumber MR, Patel HV, Godara SM, *et al*. Post-renal transplant cytomegalovirus infection: Study of risk factors. Transplant Proc 2012;44:706–9.
8. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007;357:2601–14.
9. Humar A, Gillingham KJ, Payne WD, Dunn DL, Sutherland DE, Matas AJ. Association between cytomegalovirus disease and chronic rejection in kidney transplant recipients. Transplantation 1999;68:1879–83.
10. Funk GA, Gosert R, Hirsch HH. Viral dynamics in transplant patients: Implications for disease. Lancet Infect Dis 2007;7:460–72.
11. Doyle AM, Warburton KM, Goral S, Blumberg E, Grossman RA, Bloom RD. 24-week oral ganciclovir prophylaxis in kidney recipients is associated with reduced symptomatic cytomegalovirus disease compared to a 12-week course. Transplantation 2006;81:1106–11.
12. Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, Rohde F. Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: Results of a randomized clinical trial. Am J Transplant 2008;8:975–83.
13. Helanterä I, Kyllönen L, Lautenschlager I, Salmela K, Koskinen P. Primary CMV infections are common in kidney transplant recipients after 6 months valganciclovir prophylaxis. Am J Transplant 2010;10:2026–32.
14. Limaye AP, Bakthavatsalam R, Kim HW, Randolph SE, Halldorson JB, Healey PJ, *et al*. Impact of cytomegalovirus in organ transplant recipients in the era of antiviral prophylaxis. Transplantation 2006;81:1645–52.
15. Sagedal S, Nordal KP, Hartmann A, Degré M, Holter E, Foss A, *et al*. A prospective study of the natural course of cytomegalovirus infection and disease in renal allograft recipients. Transplantation 2000;70:1166–74.
16. Murray BM, Subramaniam S. Late cytomegalovirus infection after oral ganciclovir prophylaxis in renal transplant recipients. Transpl Infect Dis 2004;6:3–9.
17. San Juan R, Aguado JM, Lumbreras C, Fortun J, Muñoz P, Gavalda J, *et al*. Impact of current transplantation management on the development of cytomegalovirus disease after renal transplantation. Clin Infect Dis 2008;47:875–82.

18. Schroeder R, Michelon T, Fagundes I, Bortolotto A, Lammerhirt E, Oliveira J, *et al*. Cytomegalovirus disease latent and active infection rates during the first trimester after kidney transplantation. Transplant Proc 2004;36:896–8.
19. Bhadauria D, Sharma RK, Kaul A, Prasad N, Gupta A, Gupta A, *et al*. Cytomegalovirus disease in renal transplant recipients: A single-center experience. Indian J Microbiol 2012;52:510–5.
20. Adu D, Cockwell P, Ives NJ, Shaw J, Wheatley K. Interleukin-2 receptor monoclonal antibodies in renal transplantation: Meta-analysis of randomised trials. BMJ 2003;326:789.
21. Reusing JO, Feitosa EB, Agena F, Pierrotti LC, Azevedo LSF, Kotton CN, *et al*. Cytomegalovirus prophylaxis in seropositive renal transplant recipients receiving thymoglobulin induction therapy: Outcome and risk factors for late CMV disease. Transpl Infect Dis 2018;20:e12929.
22. Browne BJ, Young JA, Dunn TB, Matas AJ. The impact of cytomegalovirus infection ≥1 year after primary renal transplantation. Clin Transplant 2010;24:572–7.
23. von Willebrand E, Pettersson E, Ahonen J, Häyry P. CMV infection, class II antigen expression, and human kidney allograft rejection. Transplantation 1986;42:364–7.
24. Pouteil-Noble C, Ecochard R, Landrivon G, Donia-Maged A, Tardy JC, Bosshard S, *et al*. Cytomegalovirus infection-An etiological factor for rejection? A prospective study in 242 renal transplant patients. Transplantation 1993;55:851–7.
25. Sagedal S, Hartmann A, Nordal KP, Osnes K, Leivestad T, Foss A, *et al*. Impact of early cytomegalovirus infection and disease on long-term recipient and kidney graft survival. Kidney Int 2004;66:329–37.
26. Dickenmann MJ, Cathomas G, Steiger J, Mihatsch MJ, Thiel G, Tamm M. Cytomegalovirus infection and graft rejection in renal transplantation. Transplantation 2001;71:764–7.
27. Toupance O, Bouedjoro-Camus MC, Carquin J, Novella JL, Lavaud S, Wynckel A, *et al*. Cytomegalovirus-related disease and risk of acute rejection in renal transplant recipients: A cohort study with case-control analyses. Transpl Int 2000;13:413–9.
28. Peleg AY, Husain S, Qureshi ZA, Silveira FP, Sarumi M, Shutt KA, *et al*. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: A matched case-control study. Clin Infect Dis 2007;44:1307–14.