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*Original Article*

# Evaluation of cytomegalovirus infection/disease in IgG positive renal transplantation recipients on valaciclovir prophylaxis

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## Abstract

Introduction: The reactivation of CMV (Cytomegalovirus) in renal transplant recipients may be manifested across a clinical spectrum from asymptomatic viraemia to organ rejection. The purpose of this study is to evaluate the patients who have experienced CMV infection after renal transplantation in the last twelve years, and to assess the efficacy of valacyclovir.

Methodology: Renal transplant recipients' demographic, clinical and laboratory data were evaluated retrospectively between 2006-2018. Valaciclovir was given at the standard prophylaxis dose of 2000 mg/daily. CMV Polymerase Chain reaction (PCR) was performed in 2-week intervals until 1 year after transplantation, and upon any symptoms attributable to CMV.

Results: The entire study group had D+/R+ (donor–positive, recipient-positive) serological status of the CMV virus. 171 (59.2%) patients had only CMV infection, 60 (20.8%) had overall CMV antigen positivity until the end of the follow-up period and 7 (2.4%) patients had CMV disease. Rejection episodes were diagnosed in 31 (10.8%) patients; 20 (64.5%) of those were PCR positive for CMV; mortality rate was 12 (4.2%) but those who died had a non-CMV related disease.

Conclusions: Valaciclovir may be preferred in prophylaxis instead of valganciclovir as we used in our study since valganciclovir has prolonged treatment time, rapid development of drug resistance, drug toxicity and high cost.

**Key words:** Renal transplantation; CMV; CMV disease; Valacyclovir.

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## Introduction

Renal transplantation is a life saving procedure for patients with end-stage renal disease. However, rejection episodes and opportunistic infections remain major complications [1]. Extended use of induction therapies and intensification of maintenance immunosuppression increase infection rates. Cytomegalovirus (CMV) is one of the most common opportunistic infections after solid organ transplantation (SOT) [2]. CMV latently resides in immune progenitor cells. Disorders inducing progenitor cells naturally promote the replication of CMV [3,4]. The reactivation of CMV in renal transplant recipients may be manifested across a clinical spectrum from asymptomatic viraemia to organ rejection, decreased graft survival, and decreased immune function resulting in comorbid infections and mortality [5]. CMV disease risk is 12.3% upon administering no prophylaxis following solid organ transplant [5].

The risk factors of CMV infection are serostatus of the donor and recipient, previous rejection episodes, and intense immunosuppression [6,7]. CMV seroepidemiology in Turkey differs with the socioeconomic changes among the regions over time, whereas the rates of IgG positivity for CMV is high (91.5%-100%) [8].

Several published data suggest that universal prophylaxis may convey better outcomes compared to preemptive therapy, especially in the higher risk D+/R− (donor–positive, recipient-negative) population. Benefits of universal prophylaxis include fewer opportunistic infections (including Kaposi's sarcoma and post-transplant lymphoproliferative disease), improved graft and patient survival, lower rates of rejection, easier logistics and lower monitoring costs [9].

Universal prophylaxis entails the administration of antiviral medication to all patients, or a subset of "at-risk" patients, starting within 10 days after transplant

and continuing for a finite period (i.e., 3-6 months). Acyclovir, valacyclovir, intravenous ganciclovir, oral ganciclovir, and valganciclovir have been studied as universal prophylaxis [10-12]. Foscarnet and cidofovir are very rarely used for routine prophylaxis due to their significant level of toxicity [10-12]. Intravenous ganciclovir and CMV immunoglobulin are commonly used for the more immunocompromised transplant recipients, such as lung or heart transplant recipients [10-12]. Valganciclovir is currently the most commonly used drug for prophylaxis even though its use may result in a greater likelihood of neutropenia, side effects and higher costs [13]. Moreover, high-dose valacyclovir has been shown to be efficient in the prophylaxis of renal transplant recipients [14]. Prophylaxis proves to be effective in reducing disease; however, the optimal regimen remains uncertain.

The purpose of this study is to evaluate the patients after renal transplantation performed in our hospital in the last twelve years, and to assess the efficacy of valacyclovir.

## Methodology

All of the patients included in this study underwent renal transplantation at our hospital between 2006-2018, and were evaluated retrospectively. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the ethics committee of the Medical Faculty of Pamukkale University. Patients' demographic, clinical and laboratory data were collected from patient records in the transplantation records of the nephrology clinic. Postoperative immunosuppressive therapies were administered with interleukin-2 receptor (IL-2R) antagonist followed by triple maintenance immunosuppressive therapy including oral prednisolone, mycophenolate mofetil (MMF).

Oral valacyclovir treatment was initiated for the prevention of CMV within 10 days following the transplantation, and continued until the 100th day. Valaciclovir was given at the standard prophylaxis dose of 2000 mg/day. The antiviral prophylaxis and treatment doses were adapted to renal function. After prophylaxis, CMV PCR was performed in 2 week intervals until 1 year after transplantation, and when any symptoms attributable to CMV were observed. The CMV antibody status of donors and recipients was determined by enzyme-linked immunosorbent assay (ELISA) for anti CMV IgG.

The following tests were applied for the detection of the virus in peripheral blood: antigen phosphoprotein 65 (pp65) and polymerase chain reaction (PCR) for CMV DNA. The pp65 test is a rapid, semi-quantitative immunofluorescence assay, and the pp65 antigen data were reported as the number of pp65-positive cells per number of leukocytes infected with CMV. CMV viremia was defined as the detection of virus DNA above the lower value of the linear measuring range, and it was reported as positive detection. Linear measuring range was determined as < 250 copies/mL (the cut-off value that could be measured up to 2009) and < 150 copies/mL (the cut-off value that could be measured after 2009).

CMV disease was defined according to the definition presented in "The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation" [11]. Accordingly, CMV infection was recognized as the evidence of CMV replication regardless of symptoms (differs from latent CMV), and has been defined as "the isolation of the virus, or the detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen". CMV viremia with corresponding symptoms, or CMV tissue-invasive disease documented by molecular or histopathologic studies at tissue level was categorized as CMV disease. CMV disease can be further categorized as a viral syndrome (i.e., fever, malaise, leukopenia, and/or thrombocytopenia), or as tissue invasive disease ("hepatitis, gastroenteritis, pneumonia, retinitis"). Acute graft rejection was suspected upon acute increase of serum creatinine, and was diagnosed with the help of biopsy histology [12]. In order to determine the influence of follow up duration on CMV after the transplantation, renal recipients were divided into three groups according to their follow up duration. The first group patients consisted of those who developed primary CMV infection in the first three months, and second group consisted of patients who developed the infection between 3-6 months, and the third group consisted of patients who developed the infection after 6 months, respectively.

All the patients received *Pneumocystis jirovecii* antimicrobial prophylaxis with trimethoprim-sulfamethoxazole.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical program, version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY). The independent samples t-test was used for variables that met the assumption of normal distribution, and mean and standard deviation values were given. The Mann-Whitney U test was used for variables in which the assumption of normal

distribution was not met, and median, first and third quartile values (25-75%) were given. The Chi-square test was used to compare categorical variables. Receiver operating characteristics (ROC) curves were plotted, and cut-off points were determined to detect the probability of variables to predict mortality. According to the univariate and ROC analysis results, logistic regression analysis was performed to investigate the independent risk factors for CMV infection. Survival was analyzed by the Kaplan-Meier method. The Hosmer and Lemeshow test was used to evaluate the statistical power of the model. A value of $p < 0.05$ was considered significant.

## Results

A total of 288 renal transplantation recipients were identified during the study period. The mean follow-up duration was 72 ± 42.6 months (range: 3-152 months). The mean age of patients was 47.1 ± 12.5 (range between ages 19-78 years). 171 (59.2%) patients had only CMV infection, 60 (20.8%) had overall CMV antigen positivity until the end of the follow-up period, CMV DNA was < 150 copies/mL in 71 (24.6%) of these patients and CMV DNA was < 235 copies/mL in 14 (4.8%). The mean level of CMV DNA-emia was 762 ± 4366. Table 1 summarizes demographic characteristics of the CMV infected and non infected groups.

Dialysis modality before transplantation consisted of: 208-hemodialysis (HD) patients, 63-peritoneal dialysis (PD) patients, and 17 patients were dialyzed using either HD or PD at different times. The mean time on dialysis was 65.9 ± 63.9 (range 0-360) months. The entire study group was of D+/R+ (donor–positive, recipient-positive) serological status of the CMV virus.

In our study, most patients received basiliximab and a calcineurin inhibitor-based regimen. One hundred and sixteen (40.3%) patients (87 (50.9%) patients CMV-positive) received routine triple immunosuppression induction with basiliximab, mycophenolate mofetil and a calcineurin inhibitor (CyA/tacrolimus). One hundred and thirteen (39.2%) patients (54 patients (31.6%)

**Table 1.** Characteristics of 288 kidney transplant recipients.

| Variables | Total (n = 288) | CMV (+) (n = 171) | CMV (-) (n = 117) | *p* value |
|---|---|---|---|---|
| | | Mean (± SD) or n (%) | | |
| **Male** (%) | 170 (59) | 96 (56.1) | 74 (63.2) | 0.2 |
| **Age** (n = 288) | 46.5 ± 13.04 | 47.2 ± 11.9 (20-74) | 47 ± 13.4 (19-78) | 0.9 |
| **Transplantation age** (n = 288) | 43.6 ± 12.9 (6-67) | 40.3 ± 12.2 (15-67) | 39 ± 13.1 (6-67) | 0.4 |
| **Donor age** (n = 157) | 46.5 ± 13.04 (16-84) | 47.8 ± 12.8 (16-84) | 50.2 ± 13.5 (20-79) | 0.2 |
| **Type of kidney transplantation** (Deceased donor) (n = 288) | 77 (26.7%) | 55 (32.2%) | 22 (18.8%) | 0.014 |
| **Follow up period** (month) (n = 288) | 13.8 ± 5.2 | 84 ± 42.6 (3-152) | 12.6 ± 4.1 (3-144) | 0.04 |
| **Reason for chronic renal failure** (n = 288) | | | | 0.3 |
| HT | 54 (34.6%) | 37 (35.2%) | 17 (33.3%) | |
| DM | 10 (6.4%) | 4(3.8%) | 6 (11.8%) | |
| HT + DM | 14 (9%) | 9(8.6%) | 5 (9.8%) | |
| NSAID | 7 (4.5%) | 6 (5.7%) | 1 (2%) | |
| Glomerular disease | 20 (12.8%) | 10 (9.5%) | 10 (19.6%) | |
| Urinary tract infection | 6 (3.8%) | 6 (5.7%) | 0 | |
| Genetic anomaly | 3 (1.9%) | 2 (1.9%) | 1 (2%) | |
| Solitary kidney | 7 (4.5%) | 4 (3.8%) | 3 (5.9%) | |
| Atrophic kidney | 1 (0.6%) | 1 (1%) | 0 | |
| Polycystic kidney disease | 8 (5.1%) | 5 (4.8%) | 3 (5.9%) | |
| Nephrolithiasis | 8 (5.1%) | 5 (4.8%) | 3 (5.9%) | |
| Bleeding hypoperfusion | 1 (0.6%) | 0 | 1 (1%) | |
| Amyloidosis | 3 (1.9%) | 2 (1.9%) | 1 (2%) | |
| IgA nephropathy | 2 (1.3%) | 1 (1%) | 1 (2%) | |
| Renal cell carcinoma | 2 (1.3%) | 2 (1.9%) | 0 | |
| Neurogenic bladder | 1 (0.6%) | 1 (1%) | 0 | |
| Idiopathic | 9 (5.8%) | 9 (8.6%) | 0 | |
| **Survey** | | | | 0.09 |
| Alive | 224 (77.8%) | 138 (80.7%) | 86 (73.5%) | |
| Exitus | 12 (4.2%) | 5 (2.9%) | 7 (6%) | |
| Rejection | 31 (10.8%) | 20 (11.7%) | 11 (9.4%) | |
| Followed in external center clinic | 21 (7.3%) | 8 (4.7%) | 13 (11.1%) | |
| **BK virus positivity** | 126 (43.8%) | 87 (50.9%) | 39 (33.3%) | 0.003 |

HT: Hypertension; DM: Diabetes mellitus; NSAID: Non steroidal antiinflammatory drug; BK virüs (polyoma hominis 1).

CMV-positive) received routine triple immunosuppression with tacrolimus, mycophenolate mofetil (MMF) and oral prednisolone (Table 2). Upon comparing two immunosuppression induction regimens, basiliximab-based regimen was found to have significantly higher CMV positivity than the other regimen ($p < 0.05$). The treatment of 12 (10.1%) patients was changed during follow-up. Nine (10%) of these patients were CMV-positive.

Mortality rate was 4.2% (12 patients), and 31 (10.8%) patients returned to dialysis. Among these, 1 (0.3%) patient died of myocardial infarction, 4 (1.4%) patients died of cancer, 3 (1%) patients died of sepsis, 1 (0.3%) patient died of postoperative bleeding, 2 (0.7 %) patients died of stroke, and 1 (0.3%) patient died of infective endocarditis. None of the patients died due to CMV related diseases (Figure 1).

Rejection episodes were diagnosed in 31 (10.8%) patients, 20 (64.5%) of them were PCR-positive for CMV, but had a non-CMV related disease. The prevalence of CMV infection was 59.2%, and 7 (2.4%) patients had CMV disease. CMV DNA was < 150 copies/mL in 71 (24.6%) of CMV positive patients, and CMV DNA was < 235 copies/mL in 14 (4.8%) patients. The average time from negative result to first positivity was 54.8 ± 71.7 (range 5-450) days.

Seven (2.4%) patients had values above CMV DNA threshold and received antiviral therapy; three of the patients had CMV disease (leukopenia, and thrombocytopenia) and did not develop CMV tissue-invasive disease in the follow-up period, and viremia regressed with valganciclovir treatment. Acute rejection due to hemolytic uremic syndrome was developed in one of these patients.

In order to determine the influence of follow up duration on CMV after the transplantation, 288 renal recipients were divided into three groups according to their follow up duration. The first group consisted of 16 (5.6%) patients who developed primary CMV infection in the first three months, and second group consisted of was 22 (7.6%) patients who developed the infection between 3-6 months, and the third group consisted of 133 (46.2%) patients who developed the infection after 6 months, respectively.

We found that higher creatinine level before CMV infection and higher creatinine level at the time of infection resulted in higher incidence of infection within the first three months ($p = 0.001$, $p = 0.04$). With lower basal BUN (blood urea nitrogen) value, the viremia was determined to be negative sooner ($p = 0.02$). Higher creatinine levels at the time of the detection of CMV DNA-positivity was determined to result in higher viremia ($p = 0.05$). The level of tacrolimus during CMV infection was significantly higher than the level before the infection ($p = 0.019$).

We found that the rate of positive CMV detection was found to be significantly higher in patients with BK virus (polyoma hominis 1) positivity ($p = 0.003$). The rate of CMV positivity was found to be 2.05 times

**Figure 1.** Kaplan-Meier curves for patient survival and graft survival in patients with CMV infection during the study period.

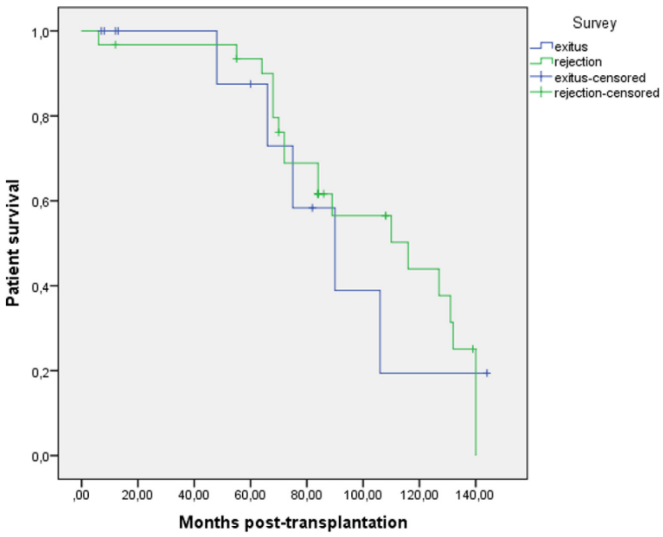


**Table 2.** Types of induction immunosuppression therapy in renal transplant recipient.

| Induction therapy | CMV positive group n = 171 (%) | CMV negative group n = 117 (%) | Total (%) n = 288 |
|---|---|---|---|
| Daclizumab Tacrolimus Mycophenolate | 16 (9.4) | 8 (6.8) | 24 (8.3) |
| Basiliximab Tacrolimus Mycophenolate | 87 (50.9) | 29 (24.8) | 116 (40.3) |
| Azathioprine Cyclosporine Prednisolone | 2 (1.2) | 5 (4.3) | 7 (2.4) |
| Sirolimus Mycophenolate Prednisolone | 0 | 4 (3.4) | 4 (1.4) |
| Azathioprine Tacrolimus Mycophenolate | 0 | 1 (0.9) | 1 (0.3) |
| Cyclosporine Mycophenolate Prednisolone | 8 (4.7) | 7 (6) | 15 (5.2) |
| Daclizumab Cyclosporine Mycophenolate | 1 (0.6) | 1 (0.9) | 2 (0.7) |
| Tacrolimus Mycophenolate Prednisolone | 54 (31.6) | 59 (50.4) | 113 (39.2) |
| Tacrolimus Sirolimus Prednisolone | 1 (0.6) | 0 | 1 (0.3) |
| Azathioprine Sirolimus Prednisolone | 1 (0.6) | 0 | 1 (0.3) |
| Everolimus Mycophenolate Prednisolone | 1 (0.6) | 3 (2.6) | 4 (1.4) |

higher in patients who received their transplants from cadaveric donors compared to live donors ($p$ = 0.01) (Table 3).

## Discussion

Optimal prevention, diagnosis and treatment of CMV infection after the transplant can significantly improve the overall outcome. Viremia is most commonly detected by either using an antigenemia assay or a QNAT (quantitative nucleic acid testing) test. The original test for viremia, CMV pp65 antigenemia, is a semiquantitative test that has been shown to be helpful in initiating preemptive therapy, the diagnosis of clinical disease, and monitoring response to therapy [3,4,15,16]. We used CMV PCR and pp65 antigenemia test for diagnosis.

The clinical manifestations of CMV range from asymptomatic viremia to CMV disease presented with fever, malasie, colitis, pneumonia, retinitis, etc [12]. In our study, we have determined that 171 (59.2%) patients had CMV DNA-positivity, and 7 (2.4%) patients with CMV disease received antiviral therapy, while three of those patients had leukopenia and thrombocytopenia. There are multiple etiologies of leukopenia and thrombocytopenia both before and after renal transplant, including host factors, medication induced myelosuppression (MMF, trimetoprim-sulfamethoxazole, valganciclovir), as well as CMV itself [17].

None of the patients with asymptomatic DNAemia developed CMV tissue-invasive disease with antiviral therapy. A recent review and meta-analysis reported that DNA-emia is predictive of CMV disease and DNAemia ensures that the disease is experienced in a significantly lower level during prophylaxis and treatment of asymptomatic CMV [9].

All of our patients were determined as D+/R+. Similar to our study group, it was demonstrated in South African renal transplant patients that the incidence of CMV disease was 32% without any prevention; and the incidence of CMV disease was 4.5% (n = 2/44) when valganciclovir prophylaxis was used [18]. In our study, the incidence level was 2.4% with valaciclovir prophylaxis. Reddy *et al.* have reported that low-dose valaciclovir prophylaxis (3 g/day) seems to be adequate for R+ patients receiving antilymphocyte therapy [19].

The type and dosage of the immunosuppressive regimen may alter the incidence and severity of CMV disease. Use of cyclosporine (CsA) increases the risk of CMV in contrast to mTOR inhibitors [20]. Immunosuppression with mTOR inhibitors instead of mycophenolate mofetil resulted in reduction in the incidence of CMV infection, syndrome and viremia in de novo renal transplant recipients [21-24]. In addition, the use of a polyclonal antibody, thymoglobulin (ATG), as induction or rejection therapy is associated with 2 to 5-fold increase in the risk of CMV infection [20,25]. Some studies have reported that basiliximab and daclizumab do not seem to increase this risk [21,25,26]. However, we found that basiliximab-based regimen resulted in significantly higher CMV positivity than other regimens ($p$ = 0.00).

As with other studies, our results showed that the highest risk of CMV infection occurred after 6 months in renal transplant recipients, due to the fact that the universal prophylaxis imparted by antiviral was stopped [18,20,21,24,25].

One of our patients experienced acute rejection due to hemolytic uremic syndrome (HUS), and our patient was using a combination of tacrolimus, basiliximab and mycophenolate mofetil. HUS/thromboticmicroangiopathy is one of the more common vascular pathologies associated with CMV and may be confused with or present with cyclosporine or tacrolimus toxicity [27-29].

Our study has several limitations. Our study was conducted retrospectively; most of the patients were D+R+ and we did not a have a comparison group of R- renal transplant receivers. Direct comparison with other studies has significant limitations given the heterogeneity in the immunosuppression regimens and baseline characteristics of the patients.

Reduction of CMV infection reduces the incidence of rejection. Valaciclovir may be preferred in prophylaxis instead of valganciclovir as we used in our study since valganciclovir has prolonged treatment time, rapid development of drug resistance, drug toxicity and high cost. Rigorous screening for other infectious etiologies should attract more attention in order to avoid the misdiagnosis of CMV disease and

**Table 3.** Univariable and multivariable logistic regression model of factors for predicting CMV infection.

| Variable | Univariable OR (95% CI) | *p* value | Multivariable OR (95% CI) | *p* value |
|---|---|---|---|---|
| Deceased donor | 2.05 | 0.013 | 1.91 | 0.027 |
| Patients with polyomavirus BK viremia | 2.071 | 0.003 | 1.97 | 0.007 |

Cytomegalovirus (CMV); BK virüs (polyoma hominis 1).

unnecessary exposure of recipients to highly toxic substances such as ganciclovir.

The prophylaxis method should be chosen in transplant programs based on local practices and experiences, including type of immunosuppression, rate of CMV seropositivity, feasibility of routine testing and cost of the medication and testing.

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## Authors' Contributions

Tugba Sari developed the theory, performed the computations, and verified the analytical methods. Belda Dursun and Mevlut Ceri supervised the findings of this work. Tugba Sari wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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