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A study of the Incidence of Cytomegalovirus Infection and Preemptive Therapy in Kidney Transplant Recipients

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Abstract
Objectives: This study aimed to determine the incidence of CVM infection and evaluate the outcome of preemptive treatment.
Methods: This prospective, two centers cohort study included recipients who underwent renal transplant between May 2019–May 2020. The incidence of CMV infection and graft outcomes were studied. All managed with preemptive therapy.
Results: In this study, 134 renal transplant recipients were recruited. Among them, 30/134 (22.4%) patients tested positive for CMV-RTPCR. We studied the impact of age on the CMV-positivity and we found that the age of the doner was associated with CMV-positivity ($P = 0.025$; OR = 0.923; CI = 0.8584–0.9943). Smoking and gender showed no association with CMV-positivity.
Conclusion: Our data suggest that the course of CMV infection is benign with a high success rate of preemptive treatment. Further evaluation for the universal prophylactic plan is needed.
Keywords: CMV, preemptive, Iraq, kidney, transplant

Introduction

CMV causes asymptomatic diseases in immunocompetent patients and it does not need specific treatment. However, it can cause serious diseases that lead to deleterious outcomes in pregnancy and immunocompromised patients such as AIDS patients and organ transplant recipients.[1-3] In organ transplant recipients including renal transplant, CMV infections are the major cause of infectious diseases morbidity and mortality with an incidence ranging from 19–90%.[4] To prevent organ rejection, organ transplant recipients are markedly immunosuppressed in the first three months after the operation.[4] This gives the opportunity for CMV to infect different organs including colon and retina.[4] Without prophylaxis or preemptive treatment, such an infection may lead to three outcomes: infectious disease syndrome; increased immunosuppression or organ rejection.[4,5] Ganciclovir and valganciclovir are the first-line medications for prophylaxis and treatment of such infections.[5] The chance of CMV infection after organ transplant is determined by the status of donor and recipient CMV serology. To prevent infections in high-risk patients (D+/R–), prophylactic medications can be given, whereas preemptive strategy can be used for moderate risk (D+/R+, D–/R+) or low risk patients (D–/R–).[4-6] Such a plan of CMV treatment and prevention is not used in some transplant centers due to economic burden and medications unavailability. This may lead to an increased rate of CMV infections and high rates of CMV resistance and relapse.[1,3,6] Post-transplant infection has been studied thoroughly in our center.[7-10] In our organ transplant center, prophylactic strategy was not used due to the expense and unavailability of the medications. The aims of this project were to determine the incidence of CVM infection and evaluate the outcome of preemptive treatment.

Materials and Methods

Study Design

This was a prospective cohort study that was conducted in Duhok and Basrah organ transplant centers between May 2019–May 2020.

Patients

In the study period, all renal transplant recipients were recruited in the study. In our center, all renal transplant recipients were managed according to the local protocol and the immunosuppressant regimen was composed of anti-thymocyte globuline (ATG) 1.5 – 2 mg/Kg at operation day and 4th day after the operation, tacrolimus 0.075 – 0.15 mg/Kg, Mycophenolate 2 g/day) and prednisolone (1 mg/kg/day then titrate to maintenance 7.5 mg/day). All renal transplant recipients were followed up in the centers. All recruited subjects were asked to visit the center monthly. In each visit, 5 CC blood was collected from the patients. Serum was separated and was kept frozen at –20˚C until CMV RTPCR was performed. No CMV prophylaxis was given to patients. Patients were tested on a monthly basis for CMV-RTPCR positivity. We followed up patients for 6 months after transplant. During the follow up, we evaluated the incidence of CMV infection, the efficacy of ganciclovir and valganciclovir, graft survival or failure. Serum creatinine and blood urea were used as indicators for graft functionality.

CMV RTPCR and IgM/IgG

CMV RTPCR was performed utilizing artus CMV RG PCR kit (Hilden, Germany) following the instructions of the manufacturer. The amplification was performed using a rotor gene real time PCR system from Qiagen (Hilden, Germany).

The patients were followed up monthly for three successive months after transplant. To determine CMV status, Elecsys CMV IgM and Elecsys CMV IgG kits were utilized (COBAS, Roche, Mannheim, Germany).

Ethics

This study was approved by the Ethics Committee in the College of Medicine, University of Zakho. Written consent was obtained from all recruited patients.

Statistics

Binary logistic regression was utilized to study the relationship between clinical outcomes and factors. All calculations were performed using Minitab 17 software.

Results

Patients

In this study, 134 renal transplant recipients were recruited. 69.4% of them were male and the mean age of our patients was 39 ± 13.3 years (Table 1). All donations came from living donors; cadaver donation was not acceptable religiously and socially. CMV serology study showed that all recipients and donors were CMV IgG positive/IgM negative.

RTPCR Positive Patients

During the follow up period, 30/134 (22.4%) patients tested positive for CMV-RTPCR. Among those, 18 (60%) were male and the average age of 39.97 ± 12.48 (Table 2). CMV-positive patients gave the history of hemodialysis of 9.8 ± 19 months (Table 2). The infection did not affect the function of the graft.

We studied factors that might impact CMV-positivity in renal transplant recipients (Table 3). We studied the impact of different diseases prior to the transplant such as hypertension, diabetes, glomerulonephritis or renal stone. We found no association between those diseases and CMV positivity. Then, we studied the impact of age on the CMV-positivity and we found that the age of the doner was associated with CMV-positivity ($P = 0.025$; OR = 0.923; CI = 0.8584 – 0.9943) (Table 3). Smoking and gender showed no association with CMV-positivity (Table 3). CMV-RTPCR became negative within a month of the treatment in 25/30 (83.33%) patients. By the end of the second month, all patients tested negative for CMV-RTPCR.

Discussion

Post-transplant CMV prophylaxis can reduce the risk of infection during the early stage after transplant operation. However, there is a concern about late onset infection after the

Table 1. **Characteristics of recipients**

Characteristics	No	%
Gender M	93	69.40
HT	108	80.60
DM	26	19.40
APCKD	7	5.22
GN	12	8.96
Stone	2	1.49
Others	25	18.66
Age (mean ± ST)	39 ± 13.3	
HD (mean ± ST)	6.88 ± 11.4	

Table 2. **Characteristics of post-transplant CMV positive**

Characteristics	No	%
Sex (male)	18	60
HT	25	83.3
DM	6	20
GN	3	10
Stone	1	3.3
Other	5	16.7
APCKD	0	0
Age	39.97 ± 12.48	
HD	9.8 ± 19	

Table 3. **Difference between post-transplant CMV positive and negatives**

Factors	CMV Negative	CMV Positive	*P*	OR	CI^{95}
Age R	38.75 ± 13.5	39.97 ± 12.48	0.66	1.01	0.9764–1.0385
Age D	29 ± 6.51	26.17 ± 5.99	0.025	0.923	0.8584–0.9943
Sex (male) R	75/104 (72.11%)	18/30 (60%)	0.2	0.58	0.2487–1.3528
Sex (male) D	70/104 (67.3%)	19/30 (63.33%)	0.68	0.83	0.3593–1.9591
HD	6 ± 7.9	9.8 ± 19	0.131	1.02	0.9927–1.0581
HT	83/104 (79.8%)	25/30 (83.33%)	0.663	1.26	0.4327–3.6989
DM	20/104 (19.23%)	6/30 (20%)	0.925	1.05	0.3791–2.9086
GN	9/104 (8.65%)	3/30 (10%)	0.822	1.17	0.2966–4.6377
Stone	1/104 (0.96%)	1/30 (3.33%)	0.39	3.55	0.2155–58.5392
Other	20/104 (19.23%)	5/30 (16.67%)	0.75	0.84	0.2861–2.4659
Smoking	74/104 (71.15%)	22/30 (73.33%)	0.82	1.11	0.4471–2.7798
APCKD	7/104 (6.73%)	0	1	0	0

discontinuation of medications. In addition, it was shown that better T-cell response and increased levels of neutralizing antibodies against the virus were developed after preemptive therapy when compared to patients who received prophylaxis.[11-13] Such an immune response that developed after preemptive therapy may prevent relapse and further CMV infections after transplant.[11-13] In this study, the CMV profile of all transplant patients was D+/R+. Prophylaxis was not given to the patients with strict follow up by CMV-RTPCR for three months. In this study, CMV-RTPCR tested positive in the first month post-transplant in 22.4% of our patients. The course of the disease was benign and did not impact the graft function. The low rate of infection might be explained by that all our patients were positive for IgG. On the other hand, the benign course of the disease can be explained by the difference in CMV genotype that may cause the disease. It was previously shown that different CMV genotypes may influence the severity and the outcome of CMV infection in organ transplant patients.[14,15] CMV genotype study has not been performed in our country, therefore more studies are recommended investigating CMV genotypes and their association with disease severity and outcomes. In contrast to other studies,[16] no association was found between age and incidence of CMV infection. In agreement with another study,[16] gender was not associated with the incidence of CMV infection. In a previous study, it was found that older donor was associated with an increased risk of CMV infection post-transplant. We found a significant relationship between younger donor age and CMV positivity. This is difficult to explain and further studies are required to investigate the impact of donor age upon CMV infection. Our study has limitations. First, this is a two centers observation study with patients all D+/R+. Second, the follow up duration was 6 months and it is unknown what the further outcome was. Our results suggested that further studies are needed recruiting D+/R– patients and the use of such an approach for those patients and longer follow up duration is needed to investigate the impact of preemptive therapy on the long-term outcome and graft survival. ■

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