

Outcomes of mTORi-involving minimized immunosuppression protocols in renal transplantation

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ABSTRACT

Aim: Immunosuppression lowering protocols are commonly involving low-dose calcineurin inhibitors (CNIs) and the mammalian target of Rapamycin inhibitor (mTORi). In renal transplant (RT) recipients, due to various factors (the development of polyoma B-K virus [BKV] and cytomegalovirus [CMV] infections, malignancy, and CNIs nephrotoxicity), immunosuppression lowering comes up mandatory. Here, we present the outcomes of renal allografts after switching from a standard immunosuppression protocol to mTORi-containing lower immunosuppression protocol.

Material and Method: This single-center, retrospective, and observational study includes RTs performed between 2014-2016. Three hundred twenty-two recipients were evaluated and 231 proper recipients were enrolled in the study. Recipients who received mTORi for at least 12 months were included in mTORi arm. Recipients who did not have a BKV and/or CMV screening test, and allograft biopsy were excluded. The remains were enrolled in mTORi-free arm. Allograft survival rate and function before mTORi and at 1, and 3-year under mTORi treatment were compared.

Findings: A total of 231 recipients were followed-up approximately for 5-years. In mTORi arm CMV and BKV viremia positivity rates were higher than mTORi-free group; $p=0.001$. Additionally, acute rejection (AR) rate was higher in mTORi arm ($p=0.001$). Estimated glomerular filtration rate (eGFR) at 1 and 3-year after mTORi arm was less than mTORi-free arm ($p=0.001$). However, 1 and 3-year recipient and allograft survival rates were similar among two groups; $p=0.23$ and $p=0.06$, $p=0.52$ and $p=0.72$, respectively.

Conclusion: In renal allograft recipients, mTORi is commonly considered in the cases that require lowering immunosuppression, such as BKV and CMV viremias, and CNI nephrotoxicity. Despite these disadvantages, it may provide a similar allograft survival rate compared to mTORi-free group. However, mTORi use is associated with more AR episodes and may not prevent the development of a worse eGFR.

Keywords: mTORi, renal allograft, renal transplantation

INTRODUCTION

Mammalian target of Rapamycin (mTOR) inhibitors; sirolimus and everolimus, are used in the kidney transplantation to prevent allograft rejection. They exert their effects via inhibiting a signaling pathway executed by mTORCs (mTOR complex 1 and 2) which results in inhibition of the immune response by disruption of the proliferation of T lymphocytes and induce immune cells apoptosis (1,2).

Calcineurin inhibitors (CNIs) are the most potent drugs in preventing acute allograft rejection in renal transplantation (RTx) recipients. However, CNIs use is associated with acute and chronic allograft

dysfunctions (3-5). The majority of immunosuppressant minimizing protocols involve CNI dose reduction and adding mTORi (5-6). Other potential factors that might have negative impacts on allograft functions are cytomegalovirus (CMV) and polyoma BK virus (BKV) infections which are directly or indirectly associated with over immunosuppression (7,8). In CMV and BKV infections, minimizing immunosuppression is the main approach of the treatment; while mycophenolate mofetil (MMF) is ceased, CNI dose is reduced and mTOR inhibitors are added (9,10). On the other hand, minimizing CNI dose is bearing acute rejection (AR)

risk, especially when is realized in the first year post-transplant (11,12). Additionally, CNIs-induced acute and chronic allograft nephrotoxicity and malignancy are two other causes that require immunosuppression lowering.

The outcomes of allografts are controversial, in minimized immunosuppression protocols, due to the variability of the study designs. In our study, we present the outcomes of the immunosuppression protocol that consists of low-dose CNI and mTORi, in RTx recipients.

MATERIAL AND METHOD

This single-center, retrospective observational study involved all kidney transplant recipients between the years 2014-2016. Data of 507 recipients were evaluated and 322 of those were enrolled in the study. A brief study design is depicted in **Figure 1**. Recipients who were on mTORi for at least 12months were enrolled in mTORi arm. Recipients who did not have BKV and CMV real-time polymerase chain reaction (PCR) testing results and at least one allograft biopsy were excluded. Recipients who have CMV and/or BKV positivity, and/or CNI nephrotoxicity but had high immunological risk were not switched to mTORi and received various treatment protocols. Those were addressed in mTORi-free arm. Early mortalities (mortality within 3 months posttransplant) and recipients with primary nonfunction grafts were excluded.

Two groups were defined as follow;

- mTORi group: low-dose CNI (target: 2-4 ng/dL for tacrolimus and 25-50 ng/mL for cyclosporine-A) + mTORi (target: 5-7 ng/dL); dose reductions were performed due to CMV, BKV positivity or CNI nephrotoxicity.
- mTORi-free group: standard dose CNI (target: 5-12 mg/dL) + MMF (1-2 gr/day). Recipients who received mTORi less than 6 months also included in this group.

Allograft functions before the onset of mTORi, 1 and, 3-year allograft functions, and allograft losses were evaluated. CMV and BKV viremias were investigated in blood samples, by using reverse transcriptase quantitative PCR. Biopsy-proven AR episodes, donors' and recipients' ages were noted.

Ethics committee approval was obtained from “The University Scientific Research and Ethic Committee” of the Yeni Yuzyl University with IRB; 2020/06-478.

Statistical Analysis

Data were analyzed by using the Statistical Package for Social Sciences (S.P.S.S.) for Windows version 15. Numeric variables were presented as mean±standard deviation, and median (minimum and maximum). Categorical variables compared by using the Chi-Square test. Parametric variables were compared among the two groups, by using independent samples T-test. Allograft and patient survival rates were analyzed by Kaplan Meier survival curves. Cox-regression was used to demonstrate the impact of the potential factors on recipient and allograft survival. $p < 0.05$ was accepted significant in a 95% confidence interval.

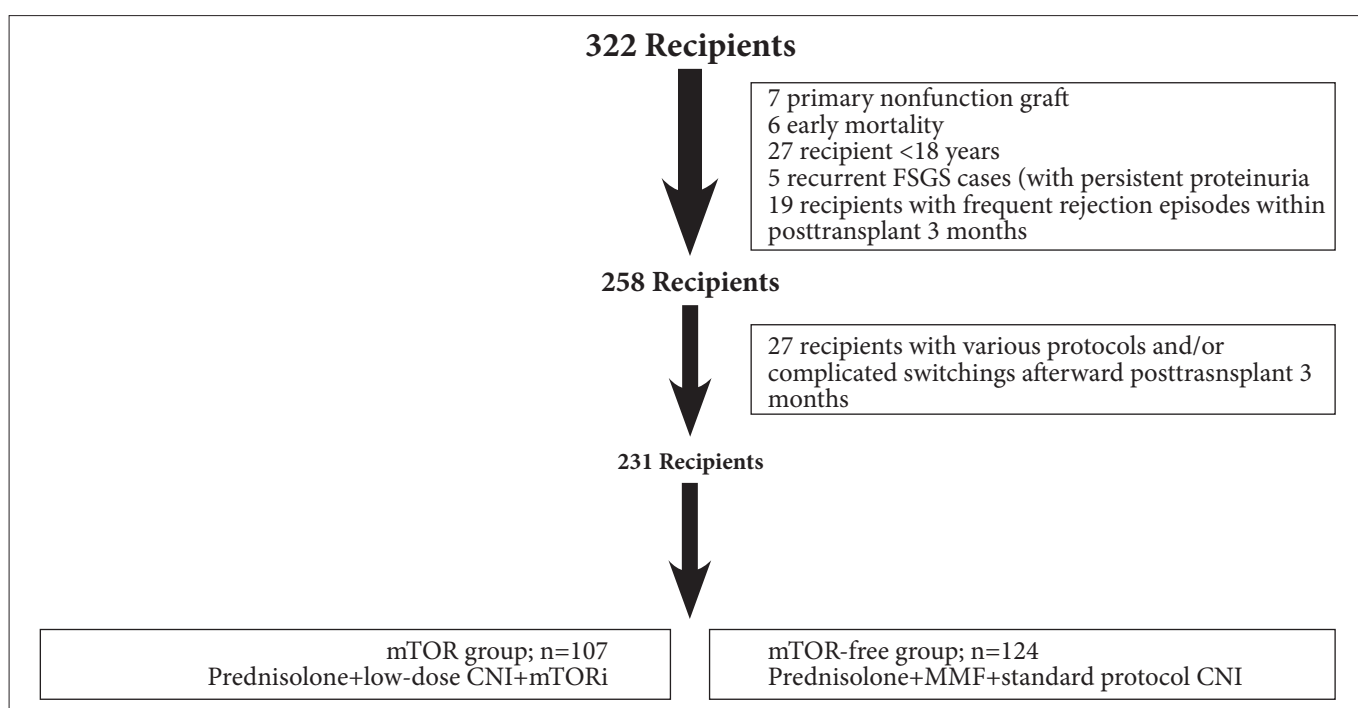


Figure 1. The recipient and allograft survival rates of two groups.

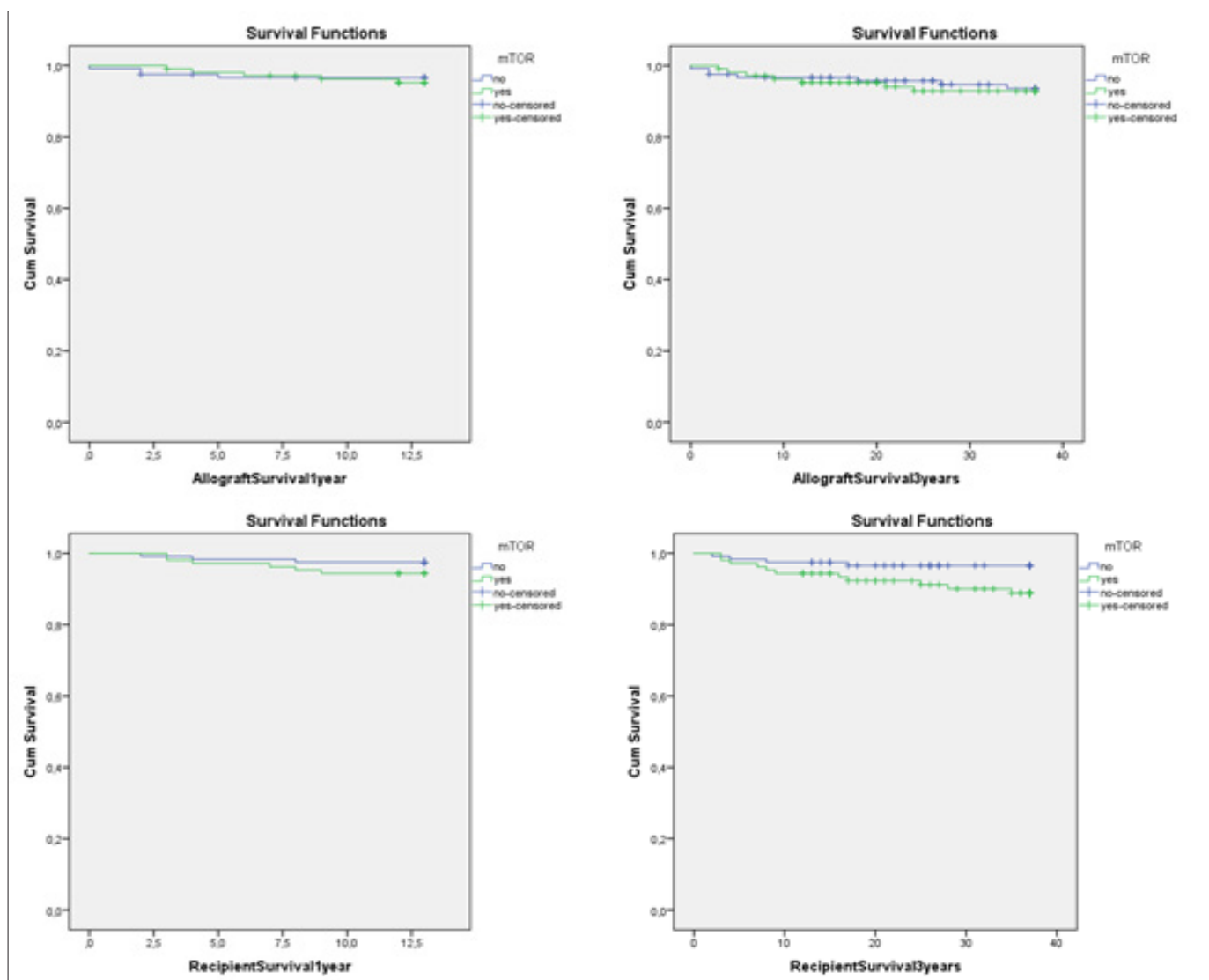
RESULTS

A total of 231 recipients, 132 males, and 99 females were evaluated, and the mean age was 45.79±11.10. One hundred-seven recipients received mTORi and 124 recipients received mTORi-free protocol. **Table 1** demonstrates the clinical and laboratory features of recipients and donors. 83.9% of the allograft donation was from living donors. 32.9% of recipients experienced at least one AR episode. The average follow-up duration was 54.82±20.23 months.

In mTORi arm, CMV and BKV infections and AR episodes were in higher rate compared to mTORi-free arm (p=0.001 for all). 89.1% of CMV and 89.5% of BKV viremias were in mTORi arm. 1 and 3-year allograft functions (eGFR) were

worse in mTORi arm (p=0.001 and p=0.001, respectively) (**Table 2**). eGFR before switching to mTORi was 57.28±22.17 ml/dk/1.73m² and was similar to the 12-month and 36-month eGFR, p=0.37 and p=0.11, respectively.

Allograft survival rates were similar in mTORi and mTORi-free arms at posttransplant 1 and 3-year (p=0.52 and p=0.72, respectively) (**Figure 2**). Cox-regression analysis demonstrated CMV and BKV viremia positivites had no impact on 1 and 3-year allograft survival rates (p=0.525 and p=0.876, p=0.982 and p=0.905) (**Table 3**). Besides AR episodes had a negative impact on 3-year allograft survival (p=0.014 and OR=3.996). Donor age had an impact both in 1 and 3-year allograft survival rates (p=0.022 and OR=1.039, and p=0.001 and OR=1.055).



	mTORi	mTORi-free	P value
Recipient survival rate;			
• 1 year	94.3%	97.5%	0.23
• 3 years	89.6%	96.6%	0.06
Allograft survival rate;			
• 1 year	92.3%	96.6%	0.52
• 3 years	90.4%	94.1%	0.72

Figure 2. Study design and case selection

FSGS; focal segmental glomerulosclerosis, mTOR; mammalian target of rapamycin, CNI; calcineurin inhibitor.

Table 1. Clinical and laboratory features of recipients and donors.	
N=231	
Male/female	132/99
Age, year	45.79±11.10
Recipient BMI, kg/m ²	24.06±4.24
Donor BMI, kg/m ²	26.20±4.15
Donor type; living/deceased	194 (83.9%)/37 (16.1%)
BKV positivity, yes/no	48 (20.7%)/183 (79.3%)
CMV positivity, yes/no	46 (19.9%)/185 (80.1%)
Acute rejection, yes/no	76 (32.9%)/155 (67.1%)
Average allograft survival, month (5-year)	47.36±24.03
Average recipient survival, month (5-year)	52.82±20.23
eGFR, ml/dk/min/1.73m ² ;	
3 months	62.38±33.26
1 year	71.21±24.87
3 years	63.06±24.09
5 years	59.28±26.43
Recipient survival rate;	
1 year	96.0%
3 years	93.3%
5 years	91.2%
Allograft survival rate;	
1 year	96.0%
3 years	93.8%
5 years	91.1%

BMI; body mass index, BKV; polyoma B-K virus, CMV; cytomegalovirus, eGFR; estimated glomerular filtration rate.

Table 2. Comparison of two groups for eGFR and risk factors			
	mTORi; n=107	mTORi-free; n=124	P value
Recipient age, year	45.63±12.01	44.86±10.20	0.602
Male/female	62/45	74/50	0.589
Recipient BMI, kg/m ²	23.75±3.92	24.06±4.16	0.662
CMV positivity, yes/no	41/66 (38.3%/61.2%)	5/119 (4.0%/96.0%)	0.001
BKV positivity, yes/no	43/64 (40.1%/59.9%)	5/119 (4.0%/96.0%)	0.001
Acute rejection, yes/no	40/67 (37.38%/62.62%)	22/102 (17.7%/82.3%)	0.001
CNI induced nephrotoxicity (biopsy proven); yes/no	28.6%/71.4%	17.4%/78.6%	0.603
eGFR, ml/dk/1.73 m ² ;			
1 year	59.36±25.69	71.85±25.72	0.001
3 years	54.41±23.21	70.96±27.00	0.001
Immunological risk assessment			
Low risk	82.4%	77.0%	0.751
High risk	17.6%	23.0%	
CNI induced nephrotoxicity			
Yes	28.6%	17.4%	0.603
No	71.4%	82.6%	

Table 3. Impact of factors on 1 and 3-year recipient and allograft survival rates.						
	CMV		BKV		AR	
	p value, 95% CI, and odds ratio					
1-year recipient survival	0.235 (0.533-13.083)	2.640	0.202 (0.061-1.809)	0.331	0.559 (0.126-3.068)	0.622
3-year recipient survival	0.872 (0.295-4.219)	1.116	0.593 (0.220-2.375)	0.723	0.943 (0.349-3.107)	1.041
1-year allograft survival	0.525 (0.298-10.696)	1.787	0.982 (0.164-5.865)	0.980	0.080 (0.865-13.136)	3.370
3-year allograft survival	0.876 (0.221-5.887)	1.140	0.805 (0.185-3.707)	0.828	0.014 (1.331-11.997)	3.996

CMV; cytomegalovirus, BKV; polyoma B-K virus, AR; acute rejection.

The one and 3-year recipient survival rates were similar in the two groups ($p=0.23$ and $p=0.06$) (Figure 2). Cox-regression analysis demonstrated CMV and BKV infections and AR episodes had no impact on 1 and 3-year recipient survival rates ($p=0.235$ and $p=0.872$, $p=0.202$ and $p=0.593$, and $p=0.559$ and $p=0.943$, respectively). However, recipient age was associated with worse 1 and 3-year recipients survival rates ($p=0.010$ and $OR=1.094$, and $p=0.001$ and $OR=1.096$, respectively).

Subgroup analysis revealed that 3-month posttransplant eGFRs were similar in mTORi and mTORi-free arm, $63.44±32.16$ vs $61.18±29.15$, $p=0.10$. However, in mTORi arm, eGFR at the switching time was lower compared to eGFR at posttransplant 3-month, $63.44±32.16$ vs $57.28±22.17$, $p=0.04$. eGFR at 1 and 3 years posttransplant in recipients with CMV and/or BKV positivity and AR episodes are compared in Table 4. 3-year eGFR was worst in CMV viremia positive recipients compared to the CMV viremia negative individuals ($p=0.005$) (Table 4). AR rates in CMV and BKV viremia positive recipients were given in Table 5.

Table 4. Estimated glomerular filtration rates at posttransplant 3, 12, and 36 months in CMV, BKV viremia positive recipients and in recipients with AR episodes.			
	3-month posttransplant eGFR	1-year eGFR	3-year eGFR
CMV;			
Negative	67.39±26.65	71.47±24.57	70.22±22.42
Positive	59.37±28.81	65.21±25.92	40.40±13.95
	$p=0.08$	$p=0.19$	$p=0.005$
BKV;			
Negative	65.45±27.53	70.93±25.29	64.31±25.30
Positive	72.49±19.18	69.19±18.58	58.08±20.11
	$p=0.11$	$p=0.68$	$p=0.61$
AR;			
No	67.91±24.99	70.68±23.10	67.89±23.46
Yes	60.59±31.45	67.33±25.11	49.88±25.22
	$p=0.06$	$p=0.38$	$p=0.11$

Table 5. Acute rejection and calcineurin inhibitor nephrotoxicity in CMV and BKV infections			
	Acute rejection rates ^a	CNI nephrotoxicity ^b	p value
CMV; positive/ negative	18.5%/11.0%	17.4%/28.6%	0.13 ^a , 0.60 ^b
BKV; positive/ negative	18.4%/7.2%	12.5%/22.7%	0.03 ^a , 0.99 ^b

DISCUSSION

Renal transplantation (RTx) is the favorable choice of treatment in end-stage kidney disease due to having better patient survival advantages. Additionally, a logical posttransplant immunosuppression therapy has vital importance, since the over-immunosuppression is related to serious life-threatening infections, malignancies, and allograft toxicity whereas low-immunosuppression is related to a higher rate of allograft rejection episodes. Clinicians commonly are forced to CNI minimizing approaches, due to BKV, CMV infections, and the existence of the evidence piece of the biopsy-proven CNI toxicity. In this study, we indicated switching to mTORi due to various compelling issues (CMV and BKV viremias and CNI toxicity) might have no adverse outcomes on allograft survival and function.

The evolution in immunosuppressants has advanced with the introduction of the CNI. CNIs have been associated with reduced AR rates over time, however, long-term allograft survival and function have not improved to a satisfactory extent (13,14). It is thought that CNI induced acute and chronic nephrotoxicity might have some adverse impact on allograft survival and function (14,15). CNI induced nephrotoxicity is at a high rate in RTx recipients, up to 94% (16). mTORi-involving immunosuppressant protocols have been used to avoid CNI induced nephrotoxicity (either CNI dose reduction or complete withdrawal of CNI). This approach carries the risk of higher AR episodes, however, the previous studies reported conflictive outcomes. Additionally, given the available studies which demonstrated antiviral activities of mTORi against BKV, make mTORi a good option in enhancing the immunosuppression modifications, both via allowing CNI dose reduction, and via its antiviral activity (17,18). Additionally, as an important part of the overall immunosuppressant dose reduction in the treatment of CMV viremia, switching to mTORi may provide some benefits. In our study, mTORi arm substantially was consisted of cases with CMV and BKV viremias positivities. One and 3-year allograft survival rates were similar in mTORi and mTORi-free groups. However, in the surviving allografts 1 and 3-year, eGFRs were worse in mTORi groups. Higher prevalences of CMV, BKV, and AR rates all might have an overall impact on reduced eGFR, in mTORi group. Subgroup analysis revealed CMV has associated with reduced 3-year eGFR.

Allograft survival rate and function depend on various potential adverse factors such as CMV and BKV infection, and acute rejection episodes. CMV is one of the most important infectious causes associated with substantial morbidity and mortality after organ transplantation (19,20). CMV prevalence has a great variation among RTx studies (ranging from 5% to 100%) due to different

population serostatus, immunosuppression protocols, and testing methods (21,22). Immunosuppression level is the most important influent on the development of CMV infection, and lowering immunosuppression along with valganciclovir/ganciclovir therapy is the main first-line approach in the disease control (20,23-25). In our cohort, CMV prevalence is 19.9%, and 89.1% of those were in mTOR group. 1-year eGFR in CMV positive and negative groups were similar. In CMV viremia positive recipients, after immunosuppression lowering and CMV disease treatment with valganciclovir/ganciclovir therapy, allograft function did not recovery at 3-year posttransplant (the worst eGFR). AR seems to have an impact on 3-year allograft functions. AR rate was higher in recipients with CMV viremia but statistically was not significant. However, the regression analysis revealed that AR episodes had an impact on the 3-year allograft survival in mTORi arm. CMV viremia and AR development are well-known and interrelated issues in RTx (26,27). However, allograft survival rates were at 1 and 3-year were similar in mTORi and mTORi-free groups, and surprisingly, CMV viremia positivity had no impact on allograft survival in our cohort. We think this preferable outcome might be associated with mTORi use and less CNI induced nephrotoxicity (biopsy-proven CNI nephrotoxicity has been found less in CMV positive recipients) (17.4% vs 28.6%). Posttransplant 1 and 3-year recipients' survival rates were also similar in both groups, and CMV viremia existence had no impact on the recipient survival.

Polyoma B-K virus (BKV) is highly prevalent in the general population with over 80% of individuals having serological positivities against BKV (28,29). BKV reactivation is a common problem after therapeutic immunosuppression in RTx. BKV viremia occurs in up to 13% of RTx and BKV associated nephropathy prevalence is approximately 10% (30-32). The prolonged persistent BK viremia is associated with the development of ClassII donor-specific antibodies and higher AR rates (33,34). BKV nephropathy has been associated with reduced 3-year overall allograft survival (35). The immunosuppression level is the main promotor factor in the development of BK viremia, and lowering immunosuppression (dose adjustment, drug withdrawal, substituting with another drug) is the key point of the treatment (36). In our cohort, BKV prevalence is 20.7%, and 89.5% of the cases were in mTORi arm. One and 3-year allograft and recipient survival rates were similar among BKV viremia positive and negative recipients. Cox-regression analysis revealed that BKV had no impact on overall allograft and recipient survival. AR rates were found higher in BKV positive recipients, as previous studies reported.

CONCLUSION

The low-dose CNI + mTORi protocol which is established due to many mandatory factors, has not worse outcomes compared to the protocols involving standard dose CNI.

Limitations of the study; the treatments of CMV and BKV infections and AR episodes and the impacts of the success or failure of those treatment protocols were not included in the study. Additionally, lacking assessment of the induction protocols, of the immunological risk, and of the adverse drug reactions were some other limitations of the study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The University Scientific Research and Ethic Committee of the Yeni Yuzyil University; 2020/06-478.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: Mehmet Emin Demir: Project designer, writer, coordinator, Ozgur Merhametsiz: Data collection, Murat Sevmis: Statistical analyzes, Murathan Uyar: Advisor, Sema Aktas: Advisor, Sinasi Sevmis: Advisor

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