Original Article

Comparing the Effect of Immediate versus Delayed Initiation of Tacrolimus on Delayed Graft Function in Kidney Transplant Recipients: A Randomized Open-label Clinical Trial

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ABSTRACT

Objective: Delayed graft function (DGF) is an early complication after kidney transplantation with negative impact on allograft outcomes. This study assessed the effect of delayed initiation of tacrolimus as a nephrotoxic drug, on DGF occurrence and allograft function. **Methods:** This randomized, open-label clinical trial was conducted on kidney transplant recipients with the age of at least 14 years who underwent the first kidney transplantation from deceased or living donor. Patients were randomly allocated to immediate (n = 26) or delayed tacrolimus (n = 27) groups. All patients received thymoglobulin as induction therapy and similar maintenance immunosuppression including tacrolimus, mycophenolate, and prednisolone with the difference in the time of initiation of tacrolimus either on the day of transplantation (immediate tacrolimus group) or day 3 after transplant (delayed tacrolimus group). **Findings:** DGF incidence (46.15% vs. 37.04%; P = 0.501) and duration (9.75 ± 6.41 vs. 8.6 ± 6.16 days; P = 0.675) were not different between the immediate and delayed tacrolimus groups. Estimated creatinine clearance using Cockcroft–Gault equation (63.14 ± 18.81 vs. 58.19 ± 19.42 mL/min in immediate and delayed tacrolimus groups respectively; P = 0.373) and estimated acute rejection-free survival were also comparable between the groups over the 3 months of follow-up. Compared with the immediate group, the delayed tacrolimus group showed higher estimated 3-month grafts' survival (100% vs. 84.27%; P = 0.072). **Conclusion:** Delayed initiation of tacrolimus after kidney transplantation under the umbrella of thymoglobulin induction did not result in either lower incidence or duration of DGF or improved the level of graft function in kidney transplant recipients but non-statistically significant increased 3-month grafts' survival.

Keywords: *Delayed graft function, delayed Tacrolimus, immediate Tacrolimus, kidney transplantation*

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Introduction

Delayed graft function (DGF) is a known early complication after kidney transplantation. DGF mostly affects kidney transplant recipients from deceased donors and occurs with the frequency of 20%–50% depending on the definition.[1] DGF has detrimental effect on short-term graft outcomes and also may be associated with poor long-term grafts' survival, irrespective of allograft rejection episodes.[2,3]

DGF is most often defined as the need for at least one dialysis session within the 1st week after transplantation. Definitions based on serum creatinine concentrations have also been used in the clinical studies.[4,5] DGF is

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mainly the result of ischemia and reperfusion (IR) injury and subsequent acute tubular necrosis due to multifactorial pretransplant and postischemic events.[6]

Calcineurin inhibitors (CNIs; cyclosporine and tacrolimus) are the cornerstone of maintenance immunosuppression therapy in kidney transplantation. CNIs caused graft dysfunction in animal models of IR injury due to a direct afferent arteriolar vasoconstriction mediated by the stimulation of endothelin-1 production and activation of the renin–angiotensin system and several other mechanisms.[7,8]

Although it has been proposed that avoiding CNIs during early posttransplant days may decrease IR injury and accelerate renal function recovery,[6] there are scarce clinical studies regarding the effect of delayed CNIs initiation after kidney transplantation on DGF occurrence and graft function.[9,10]

This study was designed to further increase our knowledge and evaluate the effect of delayed initiation of tacrolimus under the umbrella of a potent induction regimen using rabbit thymoglobulin on DGF occurrence.

Methods

This 1-year, prospective, randomized, open-label clinical trial was conducted in kidney transplant ward of Imam Khomeini Hospital Complex affiliated to Tehran University of Medical Sciences, Tehran, Iran, from April 2016 to April 2017.

The Local Ethics Committee approved the study protocol (IR.TUMS.REC.1395.2575). The study was registered in the Iranian Registry of Clinical Trials (IRCT201604253043N11). This study was conducted in accordance with the Declaration of Helsinki of 1975 as revised in 2013. All participants signed written informed consent forms.

Patients with the age of at least 14 years who underwent the first kidney transplantation from deceased or living donor and received thymoglobulin as induction therapy and tacrolimus, mycophenolate, and prednisolone as maintenance immunosuppression were eligible for inclusion. Patients who were candidate for multiorgan transplant, known case of malignancy, or who developed severe secondary illness immediately after transplantation were not included in the study. Patients were also excluded if any changes were performed in their maintenance immunosuppression regimen during the study.

Eligible patients were randomized using block randomization with block sizes of four to either immediate or delayed tacrolimus groups [Figure 1]. Patients in the immediate group received tacrolimus (Prograf®, Astellas Pharma, The Netherland) from the day of transplantation while patients in the delayed tacrolimus group started tacrolimus from the day 3 after transplantation. The doses of tacrolimus were adjusted to reach intended whole-blood trough level of 8–10 ng/mL for the first 3 months after transplantation according to the center's protocol in both arms of the study unless changes became necessary due to adverse effects. Other immunosuppressive therapy was the same between the two groups.

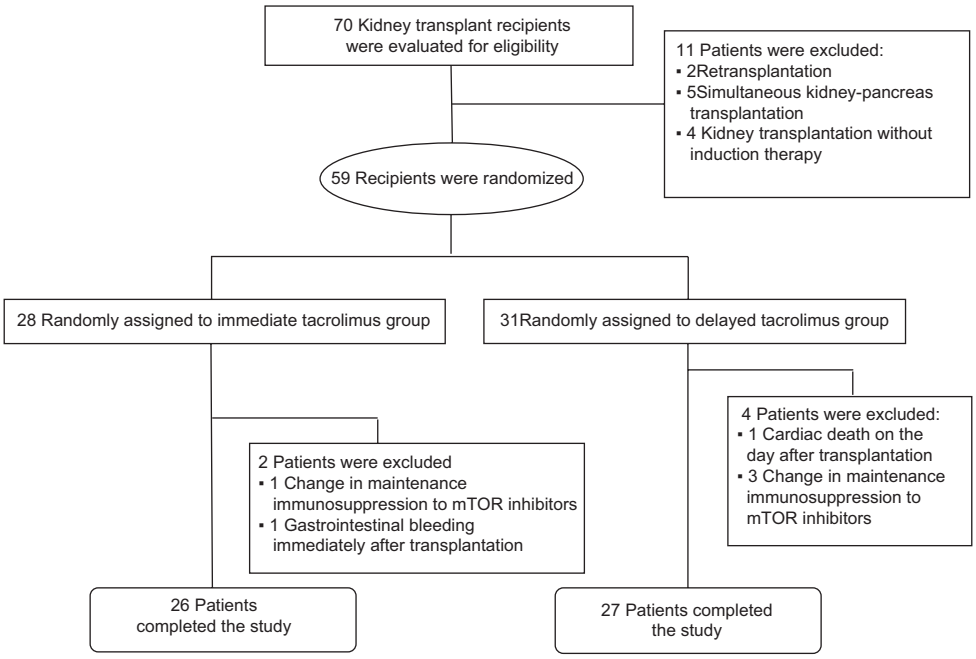

Figure 1: Patients' screening, randomization, and follow-up
mTOR = mammalian target of rapamycin

All participants received a similar immunosuppressive regimen according to the center's protocol. All patients in both groups received induction therapy using thymoglobulin at a dose of 1 mg/kg starting 1 h before transplantation surgery and continued daily to the cumulative dose of 3–4 mg/kg. Thymoglobulin dose increased in patients with prolonged DGF. All patients received intravenous methylprednisolone 500 mg at the time of transplantation that followed by daily doses of 250 and 125 mg for the first 2 days after transplantation. After that, oral prednisolone was started at daily dose of 1 mg/kg and was rapidly tapered down to 5 mg/day at the end of month 1 after transplantation. Mycophenolate mofetil was administered at the dose of 1 g several hours before transplantation. Maintenance mycophenolate mofetil was started on the day after thymoglobulin cessation at the dose of 1.5 g/day and adjusted based on white blood cells and platelet counts.

Trimethoprim/sulfamethoxazole, ganciclovir/valganciclovir, and clotrimazole troche were administered for prophylaxis of *Pneumocystis jirovecii*, cytomegalovirus, and candidiasis, respectively, for the duration defined by our center's protocol.

Each episode of clinically suggested or biopsy-proven acute rejection (BPAR) was treated with acute cellular or antibody-mediated rejection treatments such as glucocorticoid pulse, thymoglobulin, intravenous immunoglobulin, plasmapheresis, or rituximab as required.

Demographic and main clinical/laboratory data of the recipients, donors, and surgery conditions including risk factors for DGF[11] were gathered. Sex, age, body mass index, history of diabetes mellitus or hypertension of recipients and donors along with the cause of end-stage renal disease, type and duration of dialysis, panel reactive antibody and history of pretransplant transfusion in recipients, type of donor (deceased or living donor), cause of death of deceased donor, terminal serum creatinine level of the donor, and cold ischemic time of transplanted kidney were recorded. Expanded criteria donor (ECD) as a risk factor for DGF was defined as deceased donor who aged more than 60 years or aged 50–59 years with two other risk factors including serum creatinine concentration of more than 1.5 mg/dl, history of systemic hypertension, or death as a cause of cerebrovascular accident.[11]

Recipients' urine output, serum creatinine concentrations, serum electrolytes, and tacrolimus whole-blood trough levels were evaluated daily until discharge from the hospital.

Protocol biopsy was not done in our center. If the patient showed increase in serum creatinine concentration that was not justified with infection or urinary leak or obstruction, indication biopsy was performed based on patient's satisfaction and physician's decision.

After hospital discharge, all patients were monitored weekly during the 1st month after transplantation and biweekly thereafter to month 3 after transplantation regarding their serum creatinine concentrations, tacrolimus whole-blood trough levels, possible episodes of acute allograft rejections, infections, or other complications.

The primary endpoints of the study were comparisons of DGF incidence and duration between the two groups. In this study, three criteria were used to define DGF including the need for dialysis within the 1st week after transplantation, daily decrease of <10% in serum creatinine concentration during 3 consecutive days within the 1st week posttransplantation, or urine output of <300 mL within 6 h after transplantation.[5,12] The hemodialysis was ordered based on clinical judgment by medical team. DGF duration was defined as the number of days from the transplantation to the last session of hemodialysis or the day that serum creatinine levels started to decrease more than 10% per day.

Estimated creatinine clearance using Cockcroft–Gault equation at month 3 after transplantation, incidence of acute allograft rejection during the first 3 months after transplantation, 3-month patients' and grafts' survivals, and infection episodes were considered as secondary outcomes.

Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 21.0; SPSS Inc., Chicago, Illinois, USA). The normality of distributions of continuous variables was tested by the Kolmogorov–Smirnov test. Results were reported as mean ± standard deviations (SDs) or median (minimum–maximum) based on variables' distributions. Between-group comparisons of continuous variables were performed using independent Student's *t*-test or Mann–Whitney U-test which appropriate. To compare outcomes with more than one assessment point during the study course, repeated measure ANOVA was used. Kaplan–Meier log-rank test was used to analyze 3-month patients' and grafts' survivals and estimated acute rejection-free survival. Categorical variables were compared between groups using Chi-square test. $P < 0.05$ was considered as statistically significant.

Results

Patients' screening and randomization to the study have been shown in Figure 1. Of 70 screened kidney transplant recipients, 53 patients (26 patients in the

immediate and 27 in the delayed tacrolimus group) completed the study and were included in data analysis. There was no significant difference between the two groups of the study regarding study withdrawal after group allocation ($P = 0.465$).

As shown in Table 1, there was no significant differences based on independent Student's *t*-test and Chi-square test as appropriate, between the two groups at baseline characteristics of kidney transplant recipients and donors that may be risk factors for DGF such as recipients' and donors' age and sex, recipients' hemodialysis duration, donors' serum creatinine concentrations or cause of death, distribution of ECD, and organ cold ischemia time.

There was no significant difference between the two groups regarding maintenance immunosuppression regimen including tacrolimus dose and whole-blood concentration during the study period using independent Student's *t*-test or Mann–Whitney U-test, [Table 2]. However, patients in the immediate tacrolimus group were administered significantly higher cumulative doses of thymoglobulin in the induction phase of the immunosuppression therapy (5.54 ± 1.49 mg/kg vs. 3.57 ± 1.62 mg/kg; $P < 0.001$).

DGF incidence among all participants who completed the study was 41.5% considering all three DGF definitions and 22.6% based on dialysis-need definition. Occurrence of DGF based on any definition including dialysis requirement, creatinine reduction ratio, and posttransplant urine output was not statistically different between the two groups of the study. However, according to the Chi-square test, we detected slightly (9%) lower incidence of DGF in delayed tacrolimus group. There was no significant difference regarding DGF duration

Table 1: Baseline characteristics of kidney transplant recipients and donors

Characteristic	Immediate tacrolimus group (*n*=26)	Delayed tacrolimus group (*n*=27)	*P*
Recipients			
Age (years)	40.85±14.31	43.85±14.36	0.449
Sex (male), *n* (%)	17 (65.38)	18 (66.66)	0.922
BMI (kg/m^2)	24.0±4.97	23.58±4.49	0.748
Cause of ESRD, *n* (%)			0.194
Hypertension	9 (34.61)	12 (44.44)	
Diabetes mellitus	0	5 (18.51)	
Glomerulonephritis	3 (11.53)	2 (7.4)	
ADPKD	3 (11.53)	4 (14.81)	
Vesicoureteral reflux	2 (7.69)	1 (3.7)	
Other causes	9 (34.61)	3 (11.11)	
Type of dialysis, *n* (%)			0.079
Hemodialysis	20 (76.92)	22 (81.48)	
Peritoneal dialysis	0	3 (11.11)	
Preemptive transplant	6 (23.07)	2 (7.40)	
Duration of dialysis (months)	24 (3-60)	18 (3-132)	0.936
History of blood transfusion, *n* (%)	1 (3.84)	0	0.322
Panel reactive antibody (%)	0 (0-10)	0 (0-8)	0.113
Cold ischemia time (min)	281.25±184.65	231.0±175.28	0.505
Recipient-donor sex match (%)	14 (53.84)	13 (48.14)	0.678
Donors			
Type, *n* (%)			0.245
Deceased	24 (92.30)	22 (81.48)	
Living	2 (7.69)	5 (18.51)	
Age (years)	37.62±14.65	36.11±13.35	0.698
Sex (male), *n* (%)	15 (57.7)	18 (66.67)	0.50
BMI (kg/m^2)	25.93±3.38	24.91±2.92	0.264
SCr (μmol/L)	103.43±29.17	104.31±30.94	0.915
Hypertension	3 (11.53)	4 (14.81)	0.725
Diabetes mellitus	1 (3.84)	2 (7.40)	0.575
Donation after cardiac death, *n* (%)	0	2 (7.40)	0.157
ECD, *n* (%)	5 (19.23)	2 (7.40)	0.268

Data have been presented as mean±SD, median (minimum-maximum) or *n* (%) as indicated. ADPKD=Autosomal dominant polycystic kidney disease, BMI=Body mass index, ESRD=End stage renal diseases, ECD=Expanded criteria donor, SCr=Serum creatinine concentrations, SD=Standard deviation

between the two groups based on independent Student's *t*-test [Table 3].

As shown in Table 3, immediate and delayed tacrolimus groups had comparable creatinine clearance at the time of hospital discharge and at the end of month 3 after transplantation using independent Student's *t*-test. The differences of creatinine clearance also were not statistically significant at both evaluation times in patients who experienced DGF. Creatinine clearances were comparable over the evaluation times of the study across the immediate and delayed tacrolimus groups using repeated measure ANOVA ($F_{(2.37,111.16)}$ = 1.33; P = 0.270); [Figure 2].

According to the Chi-square test, the occurrence of clinically suggested acute rejection was similar between both arms of the study [Table 4]. Only 15 patients (eight patients in the immediate tacrolimus group and seven patients in the delayed tacrolimus group) underwent indication biopsy. Incidence of BPAR over the study period was not significantly different between the two groups although the trend was toward the higher episodes in the immediate tacrolimus group [Table 4]. Estimated acute rejection-free survival over the study follow-up based on Kaplan–Meier log-rank test was also comparable in the immediate and delayed tacrolimus groups (64.92% vs. 63.44% respectively; P = 0.983).

During the 3 months after transplantation, three patients in the immediate tacrolimus group experienced graft loss due to acute rejection and returned to hemodialysis treatment, while no graft loss was detected in the

Table 2: Comparison of immunosuppression components

Immunosuppression components	Immediate tacrolimus group (*n*=26)	Delayed tacrolimus group (*n*=27)	*P*
Tacrolimus dose during 1st week after transplant (mg/kg/day)	0.08±0.01 (0.08 [0.06-0.10])	0.08±0.01 (0.08 [0.06-0.10])	0.930
Tacrolimus dose during 1st month after transplant (mg/kg/day)	0.10±0.04 (0.09 [0.06-0.20])	0.10±0.04 (0.09 [0.04-0.16])	0.793
Tacrolimus dose during 2nd month after transplant (mg/kg/day)	0.09±0.03 (0.08 [0.04-0.14])	0.09±0.04 (0.09 [0.03-0.16])	0.780
Tacrolimus dose during 3rd month after transplant (mg/kg/day)	0.06±0.03 (0.06 [0.03-0.14])	0.09±0.04 (0.09 [0.02-0.18])	0.075
Tacrolimus whole-blood level during 1st week after transplant (ng/mL)	7.35±2.72 (6.40 [3.80-12.00])	7.09±3.55 (5.55 [3.70-12.90])	0.421
Tacrolimus whole-blood level during 1st month after transplant (ng/mL)	8.61±2.29 (8.30 [5.00-14.10])	8.06±2.13 (7.70 [4.20-12.80])	0.422
Tacrolimus whole-blood level during 2nd month after transplant (ng/mL)	9.24±2.21 (8.90 [5.50-14.00])	8.37±2.95 (8.80 [3.95-13.60])	0.298
Tacrolimus whole-blood level during 3rd month after transplant (ng/mL)	9.41±2.56 (9.80 [4.10-12.60])	8.26±3.03 (8.50 [4.70-14.20])	0.246

Data have been presented as mean±SD (median [minimum-maximum]). SD=Standard deviation

Table 3: Comparison of delayed graft function incidence, delayed graft function duration, and renal function in the immediate and delayed tacrolimus groups

Primary and secondary outcomes	Immediate tacrolimus group (*n*=26)	Delayed tacrolimus group (*n*=27)	*P*
Total DGF incidence, *n* (%)	12 (46.15)	10 (37.04)	0.501
DGF incidence based on dialysis, *n* (%)	6 (23.08)	6 (22.22)	0.941
DGF incidence based on SCr reduction ratio, *n* (%)	8 (30.77)	5 (18.51)	0.300
DGF incidence based on U/O, *n* (%)	3 (11.54)	6 (22.22)	0.300
DGF duration (days)	9.75±6.41 (9.5 [2-21])	8.6±6.16 (9.5 [2-19])	0.675
SCr at the time of hospital discharge (µmol/L); all patients	158.77±56.58 (150.28 [79.56-265.20])	149.57±51.36 (132.60 [70.72-247.52])	0.545
SCr at the time of hospital discharge (µmol/L); patients with DGF	201.11±45.44 (207.74 [132.60-265.20])	162.04±43.67 (159.12 [106.08-238.68])	0.062
Creatinine clearance at the time of hospital discharge (mL/min); all patients	47.91±19.10 (55.81 [15.57-87.83])	50.60±20.05 (46.72 [18.51-92.08])	0.623
Creatinine clearance at the time of hospital discharge (mL/min); patients with DGF	34.14±13.78 (32.73 [15.57-58.85])	41.00±11.25 (42.82 [18.51-56.58])	0.239
SCr at month 3 after transplantation (µmol/L); all patients	123.76±44.82 (114.92 [70.72-265.20])	125.09±35.54 (120.22 [70.72-212.16])	0.680
SCr at month 3 after transplantation (µmol/L); patients with DGF	149.93±54.98 (129.06 [93.70-265.20])	129.06±34.03 (126.85 [78.68-212.16])	0.356
Creatinine clearance at month 3 after transplant (mL/min); all patients	63.14±18.81 (67.12 [23.03-87.87])	58.19±19.42 (56.84 [27.15-92.25])	0.373
Creatinine clearance at month 3 after transplant (mL/min); patients with DGF	52.42±20.13 (48.10 [23.03-86.87])	52.50±17.88 (53.81 [27.15-79.85])	0.993

Data have been presented as mean±SD, median (minimum-maximum) or *n* (%) as indicated. DGF=Delayed graft function, SCr=Serum creatinine concentration, U/O=Urine output, SD=Standrad deviation

Table 4: Episodes of acute rejections, grafts' and patients' survival, and infectious complications during the 3 months after kidney transplantation

Secondary outcomes	Immediate tacrolimus group (*n*=26)	Delayed tacrolimus group (*n*=27)	*P*
Clinically suggested acute rejection, *n* (%)	9 (34.62)	9 (33.33)	0.922
Biopsy-proven acute rejection, *n* (%)	2 of 8 patients with available biopsy (25.00)	1 of 7 patients with available biopsy (14.28)	0.605
Graft loss, *n* (%)	3 (11.54)	0	0.069
3-month grafts' survival (%)	84.27	100.00	0.072*
3-month patients' survival (%)	90.00	100.00	0.308*
CMV infection, *n* (%)	0	2 (7.41)	0.157
BKV infection, *n* (%)	1 (3.84)	0	0.304
Bacterial infection, *n* (%)	7 (26.92)	12 (44.44)	0.184
Fungal infection, *n* (%)	1 (3.84)	0	0.304

*Kaplan-Meier log-rank test. BKV=BK (polyoma) virus, CMV=Cytomegalovirus

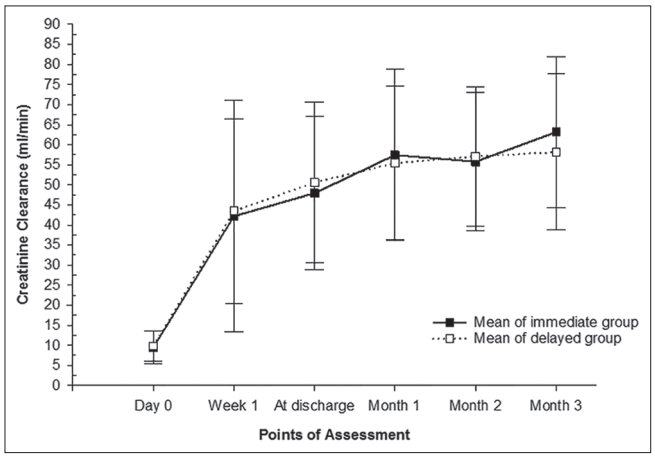

Figure 2: Creatinine clearance (mean ± standard deviation) over the study period in the immediate and delayed tacrolimus groups

delayed tacrolimus group. One patient in the immediate tacrolimus group died due to fungal infection of the central nervous system. That patient did not have functioning graft at the time of death. The estimated patients' survivals during the study period using Kaplan–Meier log-rank test were comparable in both groups [Table 4]. Estimated grafts' survivals were higher in the delayed tacrolimus group [Table 4]. According to the Chi-square test, the incidence of viral/bacterial/fungal infections did not differ between the two groups during the study [Table 4].

Discussion

In the present study, the incidence of DGF was 41.5% when all of three applied definitions of DGF were considered, while based on the dialysis criteria, 22.6% of patients experienced DGF that is comparable with DGF incidences reported by other researchers.[5] This study showed that compared to the early initiation of tacrolimus within first several hours after transplantation, delaying the administration of tacrolimus to day 3 after transplantation did not significantly reduce the incidence and duration of DGF or improve kidney function. Delayed introduction of tacrolimus resulted in 9% lower incidence of DGF based on the three criteria definition and no change of DGF incidence according to the dialysis-required definition. Among the secondary outcomes, although nonstatistically significant, BPAR episodes occurred more in immediate tacrolimus group and graft loss happened only in this group despite receiving higher cumulative doses of thymoglobulin. Since DGF is a major risk factor for inducing acute rejection,[1] higher rate of BPAR in the immediate tacrolimus group may be related to slightly higher rate of DGF in this group.

CNIs may induce afferent arteriolar vasoconstriction through increased endothelin-1 and angiotensin II concentrations and subsequent allograft impairment.[8] Despite concerns regarding CNIs-induced nephrotoxicity, there are scarce data on the association between the time of CNIs initiation after kidney transplantation and allograft function.[9,10] IR injury as a main cause of DGF occurs during the immediate phase postkidney transplantation. On the other hand, endothelin-1 as a mediator of IR injury and CNI-induced renal vasoconstriction[8,13] reaches to high level within first 3 days posttransplant in patients with DGF;[14] therefore, we delayed tacrolimus administration to day 3 after transplantation in the delayed tacrolimus group compared to days 6–7 posttransplant that has been considered in the previous studies.[9,10] In addition, those studies used anti-interleukin (IL)-2 receptor antibodies (basiliximab and daclizumab) as a mild-to-moderate induction therapy to delay CNIs initiation after transplantation.[9,10] Too delaying CNIs administration in the absence of sufficient induction therapy may induce fear of increased risk of acute allograft rejection. Although controversial, thymoglobulin versus anti-IL-2 receptor antibodies induction in kidney transplantation may result in lower incidences of DGF, acute rejection.[15-18] Therefore, in the present trial, thymoglobulin was used as an induction immunosuppression.

Kamar *et al*. showed that delaying introduction of cyclosporine to day 6 after kidney transplantation in combination with anti-IL-2 receptor antibodies resulted in a slight nonsignificant (3%) lower rate of DGF compared to early initiation of cyclosporine but no difference in the level of allograft function between the two groups.[9,19] Although nonstatistically significant, BPAR was higher in delayed compared to early cyclosporine group (26.5% vs. 15.5%).[9] Higher BPAR in delayed CNI group in that study[9] in opposed to our study may be due to using moderate potency induction therapy by basiliximab compared to high potency induction therapy by thymoglobulin in our study.

Since lower rate of graft loss and acute rejection episodes and somewhat lower nephrotoxicity have been reported by tacrolimus compared to cyclosporine,[20,21] tacrolimus is the CNI of choice and is used in our kidney transplant ward. Only one study by Andrés *et al*. assessed the effect of delayed administration of tacrolimus on the function of transplanted kidneys. In that comparative study in old kidney transplant individuals (60 years or older), delayed initiation of tacrolimus to day 7 posttransplant in the presence of induction therapy with basiliximab resulted in no difference in DGF incidence and duration, level of kidney function, and acute rejection rate compared to immediate tacrolimus administration.[10] The main confounding factor in Andrés *et al.*'s study is different induction immunosuppressive therapy between the two examined groups. They administered basiliximab induction therapy in delayed but not in immediate tacrolimus group. In fact, that study assessed the effect of induction therapy versus no induction therapy rather than the effect of CNIs timing on DGF.

This study suffers some limitations including small sample size, short period of follow-up, and single-center study. Due to thymoglobulin induction as inclusion criteria in this study that is not commonly used in kidney transplant wards of Tehran before happening DGF, including other kidney transplant centers to increase sample size was not applicable for this study.

This study showed that delayed tacrolimus initiation after kidney transplantation under the umbrella of thymoglobulin induction did not result in lower incidence of DGF, less DGF duration, or improved graft function in kidney transplant recipients but resulted in nonstatistically significant higher 3-month graft survival.

Authors' Contribution

Maryam Ghadimi: Literature search, Clinical studies, Data collection, Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

Simin Dashti-Khavidaki: Research concept, Design, Definition of intellectual content, Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

Mohammad-Reza Khatami: Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

Mitra Mahdavi-Mazdeh: Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

Mansoor Gatmiri: Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

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Neda Naderi: Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

Atefeh Jafari: Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

Mohammad-Reza Abbasi: Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

Ali Ghafari: Data analysis/interpretation, Manuscript preparation, Manuscript editing, Manuscript review and Final approval of article.

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Any similar works in the literature have addressed and discussed in the "Introduction" and "Discussion" sections of the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Wu WK, Famure O, Li Y, Kim SJ. Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. Kidney Int 2015;88:851-8.
2. Yarlagadda SG, Coca SG, Formica RN Jr., Poggio ED,

Parikh CR. Association between delayed graft function and allograft and patient survival: A systematic review and meta-analysis. Nephrol Dial Transplant 2009;24:1039-47.
3. Butala NM, Reese PP, Doshi MD, Parikh CR. Is delayed graft function causally associated with long-term outcomes after kidney transplantation? Instrumental variable analysis. Transplantation 2013;95:1008-14.
4. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant 2011;11:2279-96.
5. Mallon DH, Summers DM, Bradley JA, Pettigrew GJ. Defining delayed graft function after renal transplantation: Simplest is best. Transplantation 2013;96:885-9.
6. Schröppel B, Legendre C. Delayed kidney graft function: From mechanism to translation. Kidney Int 2014;86:251-8.
7. Inman SR, Davis NA, Olson KM, Lukaszek VA, McKinley MR, Seminerio JL, *et al.* Rapamycin preserves renal function compared with cyclosporine A after ischemia/reperfusion injury. Urology 2003;62:750-4.
8. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;4:481-508.
9. Kamar N, Garrigue V, Karras A, Mourad G, Lefrançois N, Charpentier B, *et al.* Impact of early or delayed cyclosporine on delayed graft function in renal transplant recipients: A randomized, multicenter study. Am J Transplant 2006;6:1042-8.
10. Andrés A, Budde K, Clavien PA, Becker T, Kessler M, Pisarski P, *et al.* A randomized trial comparing renal function in older kidney transplant patients following delayed versus immediate tacrolimus administration. Transplantation 2009;88:1101-8.
11. Irish WD, Ilsley JN, Schnitzler MA, Feng S, Brennan DC. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. Am J Transplant 2010;10:2279-86.
12. Daly PJ, Power RE, Healy DA, Hickey DP, Fitzpatrick JM, Watson RW, *et al.* Delayed graft function: A dilemma in renal transplantation. BJU Int 2005;96:498-501.
13. Wilhelm SM, Simonson MS, Robinson AV, Stowe NT, Schulak JA. Endothelin up-regulation and localization following renal ischemia and reperfusion. Kidney Int 1999;55:1011-8.
14. Schilling M, Holzinger F, Friess H, Seiler C, Büchler MW. Pathogenesis of delayed kidney graft function: Role of endothelin-1, thromboxane B2, and leukotriene B4. Transplant Proc 1996;28:304-5.
15. Brennan DC, Schnitzler MA. Long-term results of rabbit antithymocyte globulin and basiliximab induction. N Engl J Med 2008;359:1736-8.
16. Noël C, Abramowicz D, Durand D, Mourad G, Lang P, Kessler M, *et al.* Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. J Am Soc Nephrol 2009;20:1385-92.
17. Mourad G, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D, *et al.* Sequential protocols using basiliximab versus antithymocyte globulins in renal-transplant patients receiving mycophenolate mofetil and steroids. Transplantation 2004;78:584-90.
18. Thiyagarajan UM, Ponnuswamy A, Bagul A. Thymoglobulin and its use in renal transplantation: A review. Am J Nephrol 2013;37:586-601.
19. Mourad G, Karras A, Kamar N, Garrigue V, Legendre C, Lefrançois N, *et al.* Renal function with delayed or immediate cyclosporine microemulsion in combination with enteric-coated mycophenolate sodium and steroids: Results of follow up to 30 months post-transplant. Clin Transplant 2007;21:295-300.
20. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: Meta-analysis and meta-regression of randomised trial data. BMJ 2005;331:810.
21. Nankivell BJ, P'Ng CH, O'Connell PJ, Chapman JR. Calcineurin inhibitor nephrotoxicity through the lens of longitudinal histology: Comparison of cyclosporine and tacrolimus eras. Transplantation 2016;100:1723-31.