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Outcomes of EC-MPS combined with low-dose tacrolimus in DCD kidney transplantation for high-risk DGF recipients*

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Abstract: Effective use of immunosuppressive agents to avoid the occurrence of nephrotoxicity and rejection in recipients with delayed graft function (DGF) is a concern for physicians. We investigated the outcomes of treatment with enteric-coated mycophenolate sodium (EC-MPS) in combination with a low-dose of tacrolimus (Tac) in renal transplantation for recipients with a high risk of DGF. We conducted a retrospective study of 61 recipients with a high risk of DGF who were treated with EC-MPS and low-dose Tac. The recipients were separated into a no-DGF group and a DGF group, based on whether DGF actually occurred. The results showed that although EC-MPS and Tac doses were similar in both groups, the percentage of recipients whose mycophenolic acid area under the curve 0–12 h (MPA-$AUC_{0-12\,h}$) was below 30 (mg·h)/L was significantly higher and the Tac trough concentration significantly lower in the DGF group one week after transplantation. Notably, a higher incidence of biopsy-proven acute rejection (BPAR) was found in the DGF group and among all recipients whose MPA-$AUC_{0-12\,h}$ was less than 30 (mg·h)/L at one week after transplantation. One-year graft survival, patient survival, allograft function, and the incidence of the most common adverse events were similar in the two groups. In conclusion, the immunosuppressive regime is applicable to Chinese kidney transplant recipients, and early low exposure to EC-MPS was related to acute rejection in the recipients at a high risk of DGF.

Key words: Enteric-coated mycophenolate sodium (EC-MPS); Tacrolimus; Delayed graft function (DGF); Donation after cardiac death (DCD); Kidney transplantation
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1 Introduction

Donation after cardiac death (DCD) is becoming the main source of organ transplantation in China (Huang et al., 2015; Zhang et al., 2015), because the use of organs from executed prisoners has been banned since January 2015 and a brain death law has not been approved. The major concerns for DCD donor kidney transplantation are a high incidence of delayed graft function (DGF) and a high risk of early renal graft dysfunction and failure (Nyberg et al., 2001; Dominguez-Gil et al., 2016; Heilman et al., 2016). Physicians believe that DGF is a clinical challenge because it increases renal rejection rates and reduces graft survival (Perico et al., 2004). Therefore, the effective use of immunosuppressive agents to avoid the occurrence of nephrotoxicity and rejection is of concern to transplant clinicians when recipients are at a high risk of DGF after renal transplantation.

Currently, maintenance immunosuppressive therapy following kidney transplantation most commonly

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includes mycophenolic acid (MPA), which is the main active metabolite of both mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS) (Lu et al., 2005). To minimize nephrotoxicity, immunosuppressive regimens often incorporate a stepwise reduction of calcineurin inhibitor (CNI) exposure. MPA therapy is not associated with CNI-related acute and chronic nephrotoxicity (Salvadori et al., 2004; Kamar et al., 2006; Cortinovis et al., 2011; Sommerer et al., 2011). Therefore, increased dosage of MPA is often used to reduce the amount of CNI and to avoid nephrotoxicity. The pharmacokinetic (PK) parameters of MPA and its active metabolite MPA glucuronide (MPAG) are associated with the use of CNI. Cyclosporine A (CsA) may affect the enterohepatic circulation of MPAG, leading to an increase in the MPA area under the curve (AUC), whereas the effects of tacrolimus (Tac) on recirculation are probably less pronounced. Therefore, MPA exposure is higher in patients treated with EC-MPS plus Tac (Kaplan et al., 2005). The effect of CsA on EC-MPS PK has been extensively described in previous reports (Cortinovis et al., 2011; Stracke et al., 2012; Ding et al., 2015). Although EC-MPS is most commonly used with Tac, the safety and efficacy of this regimen need to be assessed, especially in patients at high risk of developing DGF (Budde et al., 2007; Sánchez et al., 2012).

In this study, we investigated the outcomes and PK of treatment with EC-MPS and low-dose Tac in recipients at high risk of DGF after transplantation of kidneys derived from DCD donor, during a 12-month period.

2 Materials and methods

2.1 Ethics statement

This single center, retrospective, observational cohort study was approved by the clinical research institution of the First Affiliated Hospital of Xi'an Jiaotong University, and was conducted in accordance with the provisions of the Helsinki Declaration and clinical practice guidelines. The process of organ harvesting and the transplant operations were approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University and the Red Cross Society of Shaanxi Province, and informed consent was obtained from all participants. None of the organs in this study were obtained from a vulnerable population, and there were no ethical or legal conflicts.

2.2 Study populations

The patients were recruited from July 1, 2012 to July 1, 2015 according to previous DGF prediction models (Irish et al., 2010). They were consecutive patients aged from 18 to 65 years who underwent kidney transplantation at the First Affiliated Hospital of Xi'an Jiaotong University. Recipients were excluded from the study if they (a) had undergone retransplantation, received an organ other than a kidney, or developed graft failure within 48 h of the transplant operation; (b) had a positive cross match or positive panel-reactive antibody (over 30%); or (c) had an active infection, hepatitis, or abnormal hepatic function. DCD donor inclusion criteria were as follows: (a) negative human immunodeficiency virus (HIV) antigen test; (b) 16 to 65 years of age; and (c) negative diagnosis for malignant tumor, drug abuse, and kidney disease.

2.3 Clinical definition and classification

The kidney grafts were provided by the Coordination Group of the Shaanxi Red Cross Organization, and were harvested from donors classified as controlled or uncontrolled DCDs according to the Maastricht classification (Huang et al., 2013). The diagnostic criteria for DGF are as follows: (a) dialysis is needed (at least once) in the first week after renal transplant and (b) dialysis is not used in the first week, but serum creatinine (sCr) is greater than 400 μmol/L on the 7th day after renal transplantation. Qualified patients from the entire database were divided into DGF and no DGF groups based on whether DGF occurred.

2.4 Immunosuppressive regimen

A triple immunosuppressive regimen of EC-MPS plus low-dose Tac and prednisone (Pred) was used as an initial maintenance immunosuppression treatment for all patients. The EC-MPS dose was 1440 mg/d administered within 24 h of transplantation; Tac was administered at 0.06 mg/(kg·d) beginning on the third day after transplantation. Target trough levels of Tac were 5–10 ng/ml. Pred was administered at 10 mg/d.

All recipients were treated with rabbit antithymocyte globulin (rATG) at 1.25–1.50 mg/(kg·d), with intraoperative application and for 4 d after transplantation.

2.5 Clinical assessment

Acute kidney allograft acute rejection (AR) episodes were suspected with increased sCr levels and the presence of clinical manifestations (e.g. decreased urine output, weight gain, and graft swelling pain). An allograft biopsy was performed in cases of suspected AR. All biopsies by local pathologists were evaluated according to the Banff 2005 classification (Solez et al., 2007). AR incidence, time, and therapy were recorded for 12 months after transplantation. Estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula. Adverse events (AEs) were defined as abnormal changes in physical signs, symptoms, or laboratory values. Biopsy-proven acute rejection (BPAR) cases were treated with 500 mg methylprednisolone administered intravenously for three consecutive days combined with optimized Tac and EC-MPS treatment. ATG involved treatment for 5–10 d with early higher-grade ARs and steroid-resistant ARs (Ding et al., 2014, 2015).

2.6 Efficacy and safety evaluation

Efficacy parameters were recorded for 12 months after transplantation and included: (a) AR events, (b) patient and graft survival, and (c) measurements of sCr and eGFR levels at different time points to determine renal allograft function. Safety indicators included AEs such as diarrhea, hematological abnormalities, infections, and malignancies.

2.7 PK assessment of EC-MPS and Tac monitoring

Blood samples for measuring Tac trough concentrations were drawn at 8:00 a.m. Whole blood Tac concentrations were measured using a fluorescence polarization immunoassay on an Axsym analyzer (Abbott Diagnostic, Chicago, IL, USA). At one week after transplantation, the PK profiles of MPA were assessed in both groups. Blood samples were collected before the morning medication and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 h. MPA concentrations were determined by the enzyme multiplied immunoassay technique (EMIT; Mycophenolic Acid Assay; Siemens Healthcare Diagnostic, Camberley, UK). The AUC of MPA from 0 to 12 h (MPA-$AUC_{0–12\ h}$) was calculated using the linear trapezoidal method. The blood trough concentration (C_0), minimum concentration (C_{min}), maximum concentration (C_{max}), and time to reach C_{max} (T_{max}) were determined by the concentration time curve of EC-MPS.

2.8 Statistical analysis

Baseline examination results and demographic characteristics were compared by *t*-test or *U*-test based on the normal distribution of data. For categorical data, comparisons were performed using chi-squared tests. Patient and graft survival were assessed by the Kaplan-Meier method, and compared between groups by the log-rank test. $P<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 19.0 software (SPSS Inc., Chicago, Illinois, USA).

3 Results

3.1 Clinical characteristics and demography

A total of 61 patients were finally enrolled in the study of whom 49 (80.3%) completed the 12-month follow-up. The main reasons for withdrawal were graft loss, death, conversion to immunosuppression, and loss to follow up. Demographic and clinical characteristics of the donors and recipients in the DGF (n=23) and no DGF (n=38) groups were compared, and no significant statistical differences were found between the two groups (Table 1).

3.2 PK and dosage of EC-MPS

Fig. 1a shows the MPA-$AUC_{0–12\ h}$ values at one week after transplantation in the two groups. In the DGF group, MPA-$AUC_{0–12\ h}$ was slightly lower than that in the no-DGF group, but the difference was not statistically significant ((40.45±24.11) vs. (50.58±26.46) (mg·h)/L, P=0.242) (Fig. 1a and Table 2). Mean plasma concentrations of MPA increased from pretreatment to 3 h after administration and then began to decrease in the two groups (Fig. 1a). Descriptive statistics of the EC-MPS PK parameters are summarized in Table 2. None of these parameters (C_0, C_{min}, C_{max}, and T_{max}) showed a statistically significant difference. During the 12 months of follow-up, EC-MPS dosage in both groups showed no statistically significant differences at any time point (1 week;

1, 3, 6, and 12 months) after transplantation (Fig. 1b). Although EC-MPS doses were similar in both groups, the proportion of patients with MPA-$AUC_{0–12\,h}$ below 30 (mg·h)/L was higher in the DGF group than in the no-DGF group (39.1% vs. 15.8%, P=0.0402) at one week after transplantation (Fig. 1c).

3.3 Tac dosage and exposure

Fig. 2 shows the C_0 levels and doses of Tac at various time points during the 12 months of follow-up after transplantation. At most time points, the C_0 levels were within the target exposure range, but they were slightly below the target range in the DGF group at one week after transplantation. Notably, trough levels in the DGF group were markedly lower than those in the no-DGF group (P=0.0289; Fig. 2b). However, at other time points after transplantation, Tac C_0 levels showed no statistically significant differences between the two groups.

3.4 Renal allograft function

In the no-DGF group, sCr levels decreased dramatically within one week after transplantation. However, in the DGF group, sCr levels decreased slowly to normal within one month after transplantation (Fig. 3a). eGFR displayed an opposite trend (Fig. 3b). A linear mixed effects model showed that sCr and eGFR levels at one week improved in the

Table 1 Baseline characteristics of recipients and donors

Variable	DGF group	No DGF group	P-value
Recipients (n)	23	38	
Age (year)	36.3±10.6	39.2±15.6	0.434
Gender (male/female)	14/9	22/16	0.819
Weight (kg)	66.1±19.5	64.2±17.4	0.694
BMI (kg/m^2)	23.4±3.8	22.5±4.3	0.412
Hemodialysis	21 (91.3%)	35 (92.1%)	0.711
Peritoneal dialysis	2 (8.7%)	3 (7.9%)	0.711
Primary disease			
Chronic glomerulonephritis	15 (65.2%)	27 (71.0%)	0.633
Hypertensive nephrosclerosis	3 (13.0%)	5 (13.2%)	0.705
Diabetic nephropathy	2 (8.7%)	2 (5.3%)	0.993
IgA nephropathy	3 (13.0%)	4 (10.5%)	0.908
First transplantation	23 (100%)	38 (100%)	NS
HLA mismatches	2.1±1.3	2.3±1.4	0.581
Pre-transplant PRA	2.5±3.0	2.3±3.4	0.817
Donors (n)	13	21	
Age (year)	45.2±19.4	43.6±20.3	0.822
Gender (male/female)	9/4	14/7	0.824
Weight (kg)	66.7±17.5	68.2±27.1	0.860
BMI (kg/m^2)	23.7±4.7	24.4±6.7	0.744
Primary diseases			
Craniocerebral trauma	5 (38.5%)	9 (42.9%)	0.800
Cerebrovascular diseases	6 (46.1%)	9 (42.9%)	0.851
Anoxic encephalopathy	2 (15.4%)	3 (14.2%)	0.682
Hypertension history	7 (53.8%)	10 (47.6%)	0.724
sCr before recovery (μmol/L)	161.9±53.2	132.9±73.2	0.225
Agonal time (min)	27.3±21.8	25.4±24.3	0.819
Cold ischemia time (h)	6.8±3.4	6.1±4.1	0.610
Warm ischemia time (min)	10.9±3.8	9.6±3.3	0.300

Data are expressed as mean±standard deviation or number (percentage) except recipients, donors, and gender. NS: not significant

Table 2 Pharmacokinetic and pharmacodynamic parameters of EC-MPS at one week after kidney transplantation

Group	MPA-$AUC_{0–12\,h}$ ((mg·h)/L)	MPA concentration (mg/L)			MPA T_{max} (h)
		C_0	C_{min}	C_{max}	
DGF	40.45±24.11	2.11±1.83	0.98±0.71	13.21±9.26	3.01±1.46
No DGF	50.58±26.46	1.64±1.07	1.25±1.01	14.99±10.73	2.82±1.38
P-value	0.242	0.210	0.267	0.512	0.612

Data are expressed as mean±standard deviation

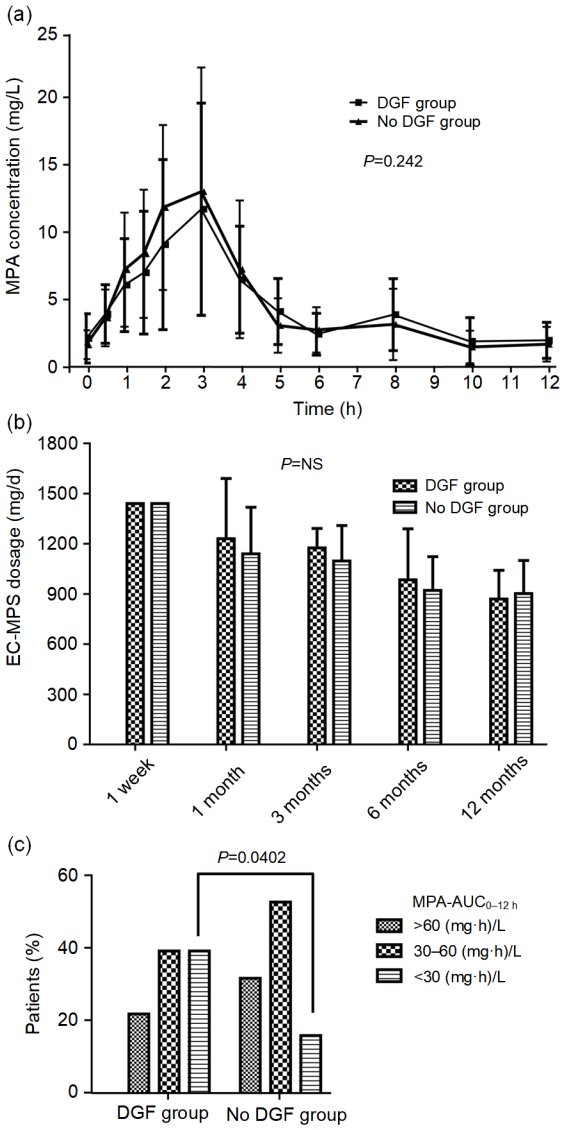

Fig. 1 EC-MPS dosage, pharmacokinetic profiles of MPA, and proportions of recipients within different MPA-AUC ranges in the two groups after kidney transplantation

(a) Pharmacokinetic profiles of MPA at one week after kidney transplantation; (b) Dosage of EC-MPS during 12 months after kidney transplantation; (c) Proportions of patients within different MPA-AUC ranges at one week after kidney transplantation. Data are expressed as mean±standard deviation

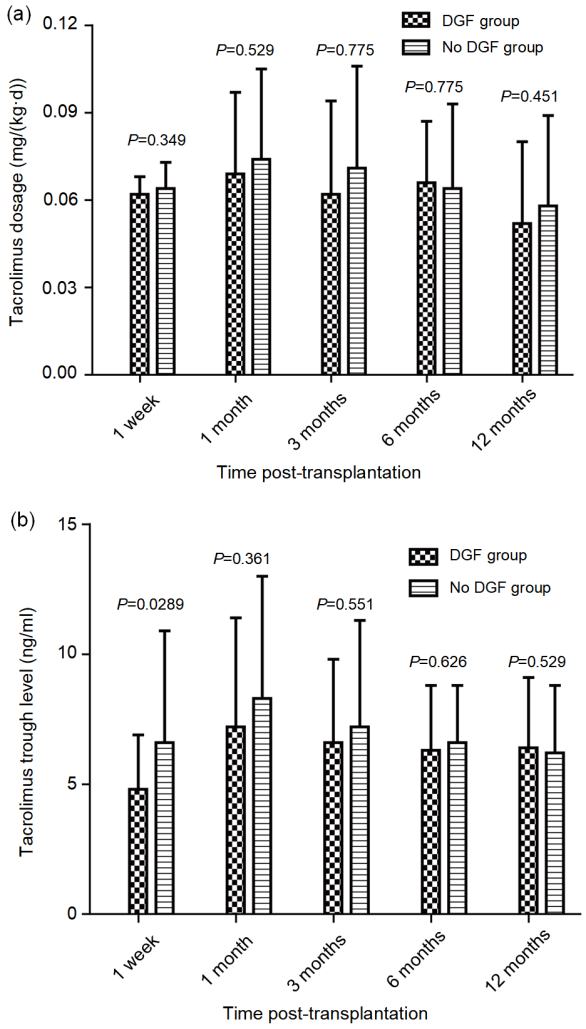

Fig. 2 Tacrolimus (Tac) dosage and blood trough concentrations (C_0) in the two groups during 12 months after kidney transplantation

(a) Mean Tac dosage; (b) Mean Tac blood trough concentrations (C_0). Data are expressed as mean±standard deviation

no-DGF group, and kidney function in most patients with DGF was restored to normal within one month after transplantation (Fig. 3).

3.5 Efficacy and safety

There was not a marked difference in the occurrence of graft loss or death between the DGF and no DGF groups (Table 3). Kaplan-Meier analysis suggested that 1-year graft survival and patient survival rates were not significantly different between the two groups (Table 3). Notably, the incidence of BPAR was significantly higher (P=0.0212) in the DGF group (30.4%) than in the no-DGF group (7.9%). Likewise, the incidence of antibody mediated rejection (AMR) was significantly higher (P=0.0417) in the DGF group (17.4%) than in the no-DGF group (2.6%) (Table 3). Interestingly, in the DGF group, when the MPA-$AUC_{0–12\,h}$ was less than 30 (mg·h)/L at one week after transplantation, the incidence of BPAR was significantly higher than that in the no-DGF group. Although there was no statistically

significant difference, the incidence of BPAR was still higher in recipients whose MPA-$AUC_{0–12\ h}$ was less than 30 (mg·h)/L than whose MPA-AUC0–12 h was more than 30 (mg·h)/L at one week after transplantation (Fig. 4). The causes of death in the DGF group were severe pneumonia (n=1) and multiple organ dysfunction syndrome (MODS, n=1); in the no-DGF group the patients died from cardiovascular accident (n=1) and severe pneumonia (n=1). The reasons for graft loss in the DGF group were unrecovered DGF (n=1) and AMR treatment failure (n=2); in the no-DGF group, graft loss was due to allograft arterial stenosis (n=1) and AMR treatment failure (n=1). The most frequently reported AEs in both groups were infections, hematologic disorders, and gastrointestinal disorders. The AEs that most frequently resulted in premature treatment discontinuation were infections, kidney dysfunction, and leucopenia. No patient discontinued the treatment because of adverse gastrointestinal events (Table 4).

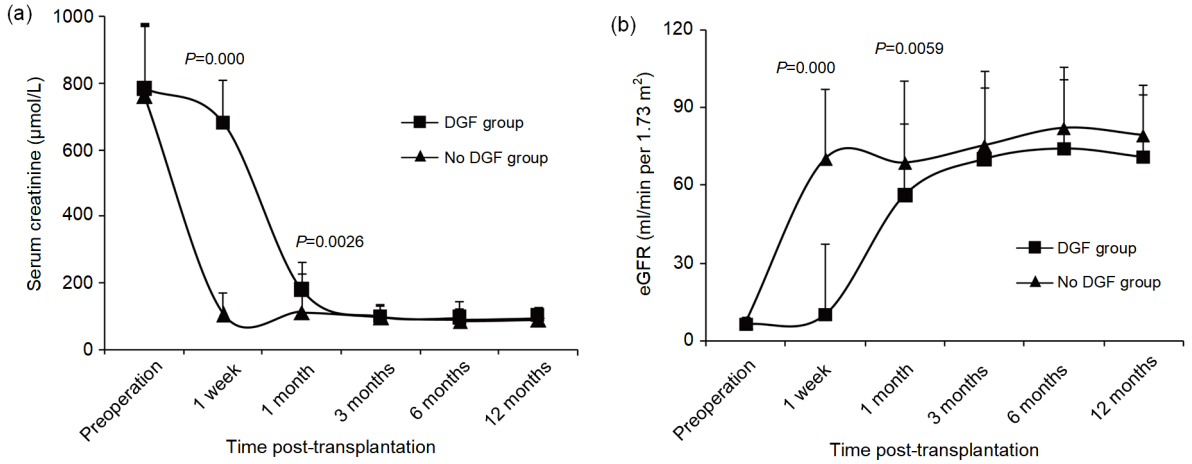

Fig. 3 Kidney allograft function in the two groups during 12 months after kidney transplantation

(a) Serum creatinine (sCr); (b) Estimated glomerular filtration rate (eGFR). Data are expressed as mean±standard deviation

Table 3 Efficacy in recipients during 12 months after kidney transplantation

Variable	Total	DGF group	No DGF group	*P*-value
Clinical diagnosis AR	10 (16.4%)	7 (30.4%)	3 (7.9%)	0.0212
BPAR	10 (16.4%)	7 (30.4%)	3 (7.9%)	0.0212
AMR	5 (8.2%)	4 (17.4%)	1 (2.6%)	0.0417
Graft loss	5 (8.2%)	3 (13.0%)	2 (5.3%)	0.5540
Death	4 (6.6%)	2 (8.7%)	2 (5.3%)	0.9930
Grafts survival (%)	91.5	86.4	94.6	0.2720
Patients survival (%)	93.2	90.9	94.6	0.5860

Data are expressed as number (percentage) except grafts survival and patients survival

Table 4 Adverse events occurring in more than 10% of recipients during 12 months after kidney transplantation

Adverse events	DGF group	No DGF group	*P*-value
Anemia	6 (26.1%)	9 (23.7%)	0.833
Leucopenia	5 (21.7%)	7 (18.4%)	0.987
Thrombocytopenia	6 (26.1%)	7 (18.4%)	0.700
Abdominal pain	4 (17.4%)	5 (13.2%)	0.937
Constipation	5 (21.7%)	4 (10.5%)	0.410
Diarrhea	4 (17.4%)	4 (10.5%)	0.705
Dyspepsia	4 (17.4%)	5 (13.2%)	0.937
Flatulence	6 (26.1%)	5 (13.2%)	0.353
Nausea	5 (21.7%)	6 (15.8%)	0.809
Vomiting	4 (17.4%)	5 (13.2%)	0.937
CMV infection	4 (17.4%)	5 (13.2%)	0.937
Respiratory tract infection	8 (34.8%)	12 (31.6%)	0.769
Pneumonia	4 (17.4%)	6 (15.8%)	0.847
Urinary tract infection	7 (30.4%)	11 (28.9%)	0.902

Data are expressed as number (percentage)

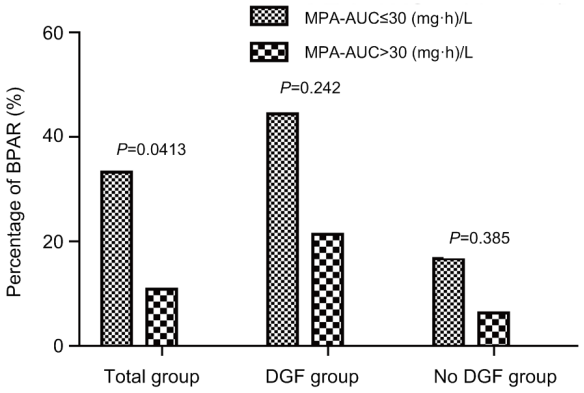

Fig. 4 Percentage of BPAR in different MPA-AUC ranges during 12 months after kidney transplantation

4 Discussion

The goals of this study were to assess the efficacy and safety of standard dose EC-MPS with low-dose Tac in recipients at high risk of DGF within one year after kidney transplantation and to calculate the PK parameters of EC-MPS to provide guidance for the use of clinical immunosuppressive agents.

In this study, higher incidence rates for BPAR and AMR were found in the DGF group (30.4% and 17.4%, respectively) compared with the no-DGF group (7.9% and 2.6%, respectively). These rates are consistent with those of other reports (Kamar et al., 2006; Singh et al., 2011), and might be caused by several factors. First, although MPA-AUC$_{0-12\ h}$, C_0, C_{min}, C_{max}, T_{max}, and EC-MPS doses showed no significant differences, the proportion of patients with MPA-AUC$_{0-12\ h}$ below 30 (mg·h)/L at one week after transplantation in the DGF group was significantly lower than that in the no-DGF group. There is an emerging consensus that individualizing MPA dosage to achieve a target MPA-AUC$_{0-12\ h}$ within the range of 30–60 (mg·h)/L provides a lower risk of AR and hematological side effects (Shaw et al., 2001; Sánchez et al., 2012). Therapeutic drug monitoring is considered important when adjusting MPA dosage to achieve optimal immunosuppressive efficacy (Arns et al., 2006; de Winter et al., 2007). In addition, Tac trough levels at one week in the DGF group were slightly lower than the targeted window and significantly lower than those in the no-DGF group. Low levels of Tac exposure may increase AR risk (Gaynor et al., 2016; Huang et al., 2016). Maintaining a low CNI level is beneficial for improving long-term kidney allograft function (Ekberg et al., 2007). This trend was observed in our study, which showed that eGFR and sCr levels at 12 months after transplantation were not significantly different between the two groups. Therefore, we recommend increasing the dose of EC-MPS within one week after transplantation to reduce the occurrence of AR in recipients at high risk of DGF. It has been reported that lower MPA-AUC values are associated with a significantly higher BPAR risk during the first 12 months after transplantation. Reanalysis of the Opticept (Gaston et al., 2009) and fixed-dose versus concentration controlled (FDCC) (van Gelder et al., 2010) trials confirmed that a lower MPA-AUC at Day 3 after transplantation was associated with a significantly higher AR rate during the first 12 months. More recently, Daher Abdi et al. (2014) reported a significant association between a low MPA-AUC, a low Tac level, and a subsequently higher risk of AR. Our findings confirm this conclusion.

There were no safety problems associated with the use of EC-MPS and low-dose Tac protocols, although slightly higher gastrointestinal AE data were reported in the DGF group compared with the no-DGF group. However, most cases of gastrointestinal disorder were mild, and discontinuation or reduction of the EC-MPS dosage as a result of gastrointestinal toxicity was rare in both groups. The average time to occurrence of gastrointestinal side effects was similar in both groups. The rates of incidence of hematological disorders and infections were similar in the two groups.

5 Conclusions

The standard EC-MPS dosage with low-dose Tac was efficacious and well-tolerated in Chinese kidney transplant recipients, and we recommend increasing the dose of EC-MPS within one week after transplantation to reduce the occurrence of AR in recipients at high risk of DGF.

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Compliance with ethics guidelines

Li-zi JIAO, Chen-guang DING, Pu-xun TIAN, Xiao-ming DING, Xiao-ming PAN, He-li XIANG, Xiao-hui TIAN, Yang LI, Jin ZHENG, and Wu-jun XUE declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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中文概要

题　目：DCD 肾移植中 DGF 高风险受者应用 EC-MPS 联合低剂量他克莫司治疗的预后分析

目　的：分析心脏死亡供体（DCD）肾移植中移植物功能延迟恢复（DGF）高风险受者应用米芙（EC-MPS）联合低剂量他克莫司治疗术后 1 年的有效性及安全性，指导临床用药。

创新点：对比 DGF 高风险受者术后发生 DGF 及正常恢复受者的免疫抑制剂药代动力学特征。

方　法：将本中心进行肾移植的 61 例 DGF 高风险受者按照实际病情纳入 DGF 组及正常恢复组，均行米芙联合低剂量他克莫司免疫抑制治疗。对比两组免疫抑制剂血药浓度及预后各项指标。

结　论：DGF 组及正常恢复组间米芙及他克莫司剂量无显著差异。术后 1 周 DGF 组 EC-MPS 血药浓度曲线下面积小于 30 (mg·h)/L 的比率显著高于正常恢复组，同时他克莫司谷浓度显著低于正常恢复组，DGF 组经活检证实的急排反应的发生率显著高于正常恢复组，术后 1 周的 EC-MPS 血药浓度曲线下面积低于 30 (mg·h)/L 的受者中经活检证实的急排反应的发生率显著高于其他受者。1 年移植物存活率、移植物功能及常见不良反应在两组间未见明显差异。

关键词：米芙（EC-MPS）；他克莫司；移植物功能延迟恢复（DGF）；心脏死亡供体（DCD）；肾移植