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Original Article

Efficacy and Safety of De Novo Everolimus Versus Mycophenolate Mofetil with Tacrolimus in Pediatric Kidney Transplantation: 1-year Follow-up

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ABSTRACT

Introduction: The efficacy and safety of everolimus (EVE) in pediatric kidney transplantation is unknown. We aimed to evaluate and compare the efficacy and safety of EVE/tacrolimus (TAC) with mycophenolate mofetil (MMF)/TAC.

Methods: This 12-month, nonrandomized single-center, open-labeled retrospective observational case-control trial included patients aged <18 years receiving kidney from a living-related or deceased donor between January 2012 and May 2017. Among 49 patients with TAC-based immunosuppression regimen, 13 received EVE/TAC regimen posttransplant, and the remaining 36 received the standard regimen using MMF/TAC. Clinical course was evaluated at 1 year.

Results: Patient characteristics between both groups were not significantly different, except for recipient age (EVE/TAC vs MMF/TAC; median: 12.7 vs 5.8 years, $p < 0.01$). Median estimated glomerular filtration rate was similar in both groups (EVE/TAC vs MMF/TAC; median: 72.3 vs 75.5 ml/min/m^2) at 1 year. Incidence of Epstein-Barr virus infection was not significantly different in both, but incidence of cytomegalovirus viremia was significantly lower with EVE/TAC than with MMF/TAC (2 of 13 [15.4%] vs 19 of 36 [52.8%], $p = 0.03$). Stomatitis rate was higher in EVE/TAC than in MMF/TAC (23.0% vs 0.0%, $p = 0.01$). While neutropenia was not statistically different in both groups, no EVE/TAC regimen did show neutropenia. Acute rejection within 1 year did not differ in both groups. Pathological vascular injury was not significantly different in both groups, despite expected vascular protection by EVE.

Conclusions: The efficacies of EVE/TAC and MMF/TAC in pediatric kidney transplantation for 1 year were comparable. Cytomegalovirus infection rate was significantly lower with EVE/TAC than with MMF/TAC regimen.

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KEYWORDS: pediatric kidney transplantation, everolimus, acute rejection, efficacy, safety

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Introduction

The regimen of combined calcineurin inhibitors (CNIs：cyclosporine [CsA] or tacrolimus [TAC]) with mycophenolate mofetil (MMF) and steroids is considered the current therapy in kidney transplantation. CNIs dramatically reduced acute graft rejection and improved short- to medium-term graft survival[1, 2]. On the contrary, their long-term use causes nephrotoxicity, malignancies, and cardiovascular diseases[3–5].

To avoid CNI toxicity, some CNI-free with everolimus (EVE) regimens were investigated, but most CNI-free regimens increased the risk for graft rejection[6, 7]. However, several studies suggested that reduced CNI with EVE regimen results in good renal function and low risk of acute rejection (AR) [8–11].

In the study of pediatric kidney transplant recipients, Tonshoff reported that EVE plus reduced TAC with steroid withdrawal regimen has preserved efficacy and safety compared with a standard TAC plus MMF with steroid regimen[12]. In contrast, Qazi reported that EVE and low-dose TAC missed noninferiority compared with MMF and standard-dose TAC based on the 10% noninferiority margin[13].

EVE has direct inhibitory effects on proliferation of smooth muscle cells, endothelial cells, and circulating vascular progenitor cells[14, 15]. Among heart transplant recipients, EVE has been associated with diminished progression of cardiac allograft vasculopathy[16]. To our knowledge, no recent study has investigated the pathology of renal allograft vasculopathy. In this study, we examined the vasculopathy between two groups to clarify the EVE plus standard TAC protocol.

Methods

Study design

This was a 12-month, nonrandomized single-center, open-labeled retrospective observational case-control trial for patients aged ＜18 years who underwent kidney transplantation. Between January 2012 and November 2017, 102 pediatric kidney transplantations were performed in our institution. Fifty-three patients were excluded because of CsA-based regimen and primary nonfunction. Forty-nine patients treated with TAC-based regimen followed over 12 months were eligible for enrolment. In case of pediatric transplantation, drug-taking adherence is another important issue. Among 13 recipients taking EVE, those who were able to take a tablet form of EVE were selected. Other 36 recipients who were unable to take tablets were given MMF (Fig. 1).

All 49 patients received an induction therapy with basiliximab on day 0 and day 4, at 20 mg in children weighing ＞35 kg and 10 mg in those weighing ＜35 kg. TAC was administered with an initial dose of 0.2 mg/kg/day with the target trough levels of 10-13 ng/ml. After transplantation, TAC target trough levels were reduced to 7-10 ng/ml at 1 month after and to 5-6 ng/ml at 3 months after transplantation. Methylprednisolone was administered at 125-250 mg/m^2 during surgery, 20 mg/day in the first week, and then reduced every 1 week according to the following protocol：16 mg/day, 12 mg/day, 8 mg/day, and 4 mg/day. In the EVE with TAC (EVE/TAC) group, EVE was started 1 week after transplantation with a dose of 1.6 mg/m^2 (＜3 mg) and target trough levels of 3-8 ng/ml, and the target trough levels were then reduced at 3-5 ng/ml at 6 months after transplantation. In the MMF with TAC (MMF/TAC) group, MMF was administered with an initial dose of 600-1000 mg/m^2/day (＜1500 mg).

Study objectives

The primary objective was to compare the efficacy of failure rate [biopsy-proven acute rejection (BPAR), graft loss, and death] at month 12 between treatment groups. BPAR was assessed by pathologist according to Banff 2013 criteria[17]. The secondary objective was to compare renal function as estimated glomerular filtration rate (eGFR) calculated using a creatinine-based equation for Japanese children and adolescents aged 2-18 years[18] and updated Schwarz formula[19] between treatment groups at 12 months. Other objectives were to compare vascular adverse events (AEs) as ah, aah, and cv of Banff 2013 classifications[17] and incidences of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and other AEs such as proteinuria and new-onset diabetes after transplantation. Growth and development were also examined.

Statistical analysis

Categorical variables were compared using the chi-square test. Continuous variables were compared using the Mann-Whitney U test. P-values less than 0.05 were considered statistically significant. To assess comparability in efficacy between the two regimens, composite efficacy failure rates between treatments were estimated with the Kaplan-Meier estimates of composite efficacy at 12 months and the difference was tested by log-rank test.

The study protocol was approved by the Ethics Com-

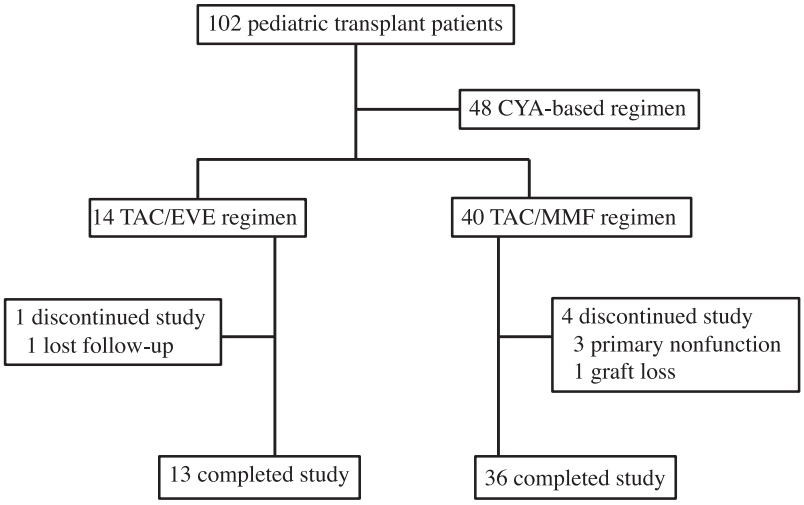

Fig. 1 Patients' disposition
CYA, cyclosporine A; EVE, everolimus; MMF, mycophenolate mofetil; TAC, tacrolimus

mittee of Toho University Omori Medical Center (No. M 19172).

Results

Study population

In this study, 49 patients were enrolled and divided into the EVE/TAC (N = 13) and MMF/TAC (N = 36) groups. Data for the 1-year follow-up were collected from all patients. Patient demographic data are shown in Table 1.

Immunosuppression

The median (first and third quartiles) EVE trough levels were 3.8 (3.6, 4.8) ng/ml at 1 month and 3.8 (3.4, 4.9) ng/ml at 1 year after transplantation. The median (first and third quartiles) TAC trough levels at 1 month were 6.7 (5.9, 7.7) ng/ml and 7.7 (6.3, 8.9) ng/ml in the EVE/TAC and MMF/TAC groups, respectively (P = .26), and 5.7 (4.7, 6.0) ng/ml and 5.0 (4.4, 5.8) ng/ml in the EVE/TAC and MMF/TAC groups, respectively (P = .48) (Table 2).

Efficacy

Clinical AR such as creatinine elevation within 1 year occurred in 0 and 3 patients in the EVE/TAC and MMF/TAC groups, respectively (P = .56). BPAR within 1 year occurred in 4 and 11 patients in the EVE/TAC and MMF/TAC groups, respectively (P = 1.00). All four episodes of T-cell-mediated BPAR in the EVE/TAC group were borderline change. In the MMF/TAC group, ten episodes of T-cell-mediated BPAR (nine borderline change, one grade 1a) and one episode of chronic antibody-mediated BPAR (Table 3) occurred. Kaplan-Meier estimates for all AR (clinical AR and BPAR) rates were 38.5% and 38.9%, respectively (log rank P = .94) (Fig. 2). No patients had a graft, and no patient died within 1 year.

Renal function

The median (first and third quartiles) eGFR at 1 year was 72.3 (59.0, 80.1) ml/min/m^2 and 75.5 (58.9, 86.8) ml/min/m^2 in the EVE/TAC and MMF/TAC groups, respectively (P = .62). The value using the updated Schwarz formula at 1 year was 77.5 (58.8, 93.3) ml/min/m^2 and 90.6 (62.8, 104.5) ml/min/m^2 in the EVE/TAC and MMF/TAC groups, respectively (P = .38).

Safety

Overall incidences of AEs and of AEs suspected to be drug-related were comparable between the EVE/TAC and MMF/TAC groups (Table 4). Except for aphthous ulcer, hyperlipidemia and other AEs were not significant in both groups, while these AEs were seen in the EVE/TAC group. The incidence of CMV disease (including CMV infection) was significantly lower with EVE/TAC than with MMF/TAC (2 [16.7%] vs 19 [51.4%], P < .05). Two patients in the EVE/TAC group developed posttransplant lymphoproliferative disorder (PTLD) or EBV viremia. These patients were seronegative for EBV prior to transplantation and received a graft from an EBV-seropositive donor. One of the EB viremia patients died because of PTLD.

Positive Banff ah score at 1 hour was recorded in 0 and 4 patients in the EVE/TAC and MMF/TAC groups, respectively (P = . 56), and no positive Banff aah and cv score at 1 hour were seen in both groups. Positive Banff ah score at 1

Table 1 Patient characteristics

	EVE/TAC (N = 13)	MMF/TAC (N = 36)
Recipient median age, y	12.7 (8.9, 14.1) *	5.8 (3.6, 12.1)
Recipient male sex, n (%)	8 (61.5)	19 (52.8)
Dialysis at Tx, n (%)	6 (46.2)	24 (66.7)
CAKUT, primary disease, n (%)	7 (53.8)	18 (50.0)
Height SDS	−1.6 (−2.6, −0.9)	−2.5 (−3.5, −1.4)
Weight SDS	−1.7 (−2.5, −0.80)	−2.3 (−3.0, −1.3)
GH therapy at Tx, n (%)	4 (30.8)	15 (41.7)
Preformed DSA, n (%)	0	3 (8.3)
Donor median age, y	42.8 (37.0-45.0)	40.5 (35.5-48.5)
Donor male sex, n (%)	5 (38.5)	19 (52.8)
Deceased donor, n (%)	0	4 (11.1)
HLA A/B/DR mismatch＜3, n (%)	5 (38.5)	19 (52.8)
CMV positive recipient, n/M (%)	8/13 (61.5)	15/36 (41.7)
CMV D+/R−, n/M (%) **	2/13 (15.4)	17/33 (51.5) *
EBV-positive recipient, n/M (%)	9/13 (69.2)	19/33 (57.6)

Continuous variables are shown as median (first quartile, third quartile)
TAC, tacrolimus; EVE, everolimus; CMV, Cytomegarovirus; EBV, Ebstein-Barr virus; n/M, number of patients among the patients with available data; DSA, donor-specific antigen; CAKUT, congenital anomalies of kidney urinary tract; Tx, transplantation; GH, growth hormone.
*P＜0.05
**Both donor and recipient CMV status were available in only a subset of patients.

Table 2 Trough levels of immunosuppressive agents

	EVE/TAC (N = 13)	MMF/TAC (N = 36)
TAC trough levels at 1 month	6.7 (5.9, 7.7)	7.7 (6.3, 8.9)
TAC trough levels at 1 year	5.7 (4.7, 6.0)	5.0 (4.4, 5.8)
EVE trough levels at 1 month	3.8 (3.6, 4.8)	
EVE trough levels at 1 year	3.8 (3.4, 4.9)	

Table 3 Observational endpoints for graft and life survival at 1 year

	EVE/TAC (N = 13)	MMF/TAC (N = 36)
Clinical rejection, n (%)	0	3 (8.3)
BPAR, n (%)		
Acute T-cell-mediated	4 (30.8)	10 (27.8)
Borderline change	4 (30.8)	9 (25.0)
Grade 1a	0	1 (2.8)
Chronic antibody-mediated	0	1 (2.8)
Graft loss	0	0
Death	0	0

year was recorded in 0 and 6 patients in the EVE/TAC and MMF/TAC groups (P = .18), and positive aah score at 1 year was recorded in 0 and 6 patients in the EVE/TAC and MMF/TAC groups (P = .31), respectively. Positive Banff cv score at 1 year was recorded in 5 and 7 patients in the EVE/TAC and MMF/TAC groups, respectively (P = .26). Positivity of Banff criteria was defined as over score 1[19].

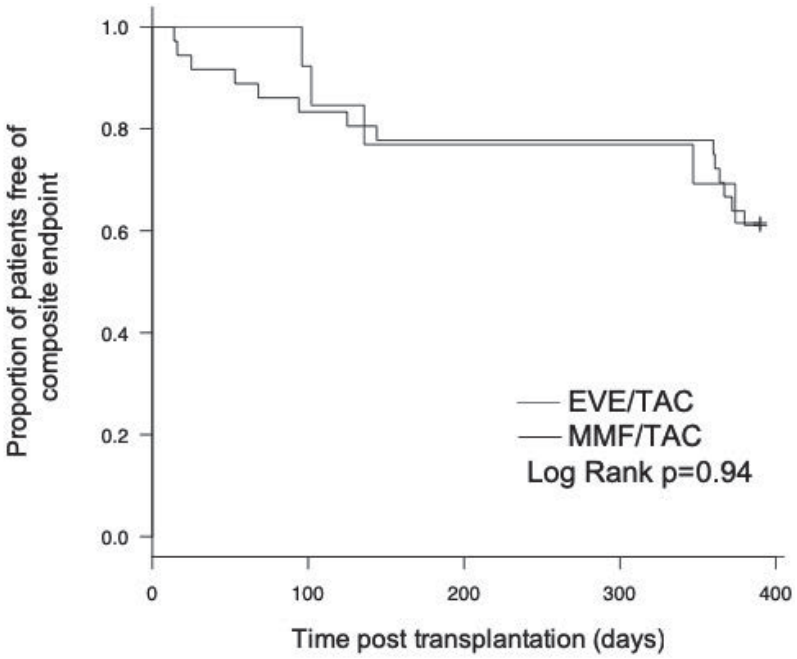

Fig. 2 Proportion of patients free from composite efficacy endpoint (BPAR and clinical acute rejection) (Kaplan-Meier estimates)

Table 4 Adverse events and infections between treatment groups, n (%)

	EVE/TAC (N = 13)	MMF/TAC (N = 36)
Hyperkalemia	0	5 (13.9)
Hypertension	4 (30.8)	11 (30.6)
Hyperlipidemia	5 (38.5) *	4 (11.1)
Hyperuricemia	1 (7.7)	2 (5.6)
Proteinuria (>0.5 g/gCre)	0	2 (5.6)
Glucose intolerance	1 (7.7)	1 (2.8)
Delayed wound healing	1 (7.7)	1 (2.8)
Neutropenia	0	4 (11.1)
Aphthous ulcer	3 (23.1) *	0
CMV viremia	2 (15.4)	19 (52.8) *
CMV disease	0	5 (13.9)
EBV infecton	2 (15.4)	0
UTI	0	1 (2.8)
Banff cv>1 within 1 year	5 (38.5)	7 (19.4)
Banff ah>1 within 1 year	0	6 (16.7)
Banff aah>1 within 1 year	0	5 (13.9)

*P<0.05

Growth

The height and weight SD score at pretransplant and 1-year posttransplant in the Japanese Society for Pediatric Endocrinology (jspe.umin.jp/medical/index.html) are shown in Table 5. All SD scores were not significantly different in both groups. The changes in height and weight SD score from pretransplant to 1-year posttransplant were not significantly different in both groups.

Discussion

In our prospective study, the eGFR at 1 year after kidney transplantation was not statistically significant in both groups. The absence of ARs in the first year after kidney transplantation with EVE/TAC regimen and the BPAR

Table 5 Growth in both groups

	EVE/TAC (N = 13)	MMF/TAC (N = 36)
Height SDS at Tx	−1.6 (−2.6, −0.9)	−2.5 (−3.5, −1.4)
Height SDS at 1 year	−1.9 (−2.2, −1.0)	−2.3 (−3.5, −1.7)
Height SDS, change	0.13 (−0.2, 0.4)	0.03 (−0.5, 0.6)
Weight SDS at Tx	−1.7 (−2.5, −0.80)	−2.3 (−3.0, −1.3)
Weight SDS at 1 year	−1.2 (−1.8, −0.6)	−2.0 (−2.7, −1.1)
Weight SDS, change	0.09 (−0.11, 0.40)	0.40 (−0.1, 1.0)

rate within 1 year after transplantation were not significant in both groups.

Only a few studies had reported about the EVE regimen in pediatric kidney transplantation. Since 2007, EVE has been used in Japan. Pape et al. reported 13 pediatric kidney transplantation cases converted from MMF to EVE with a half reduction in CsA, and prednisolone withdrawal led to eGFR decline[20]. Tönshoff et al. reported a prospective, randomized, comparative study of EVE in pediatric kidney transplant recipients, in whom renal function tended to decline with MMF with the standard dose of TAC regimen[12].

Tönshoff et al. showed similar rates of BPAR between EVE with reduced TAC and MMF with standard TAC regimen[12]. On the contrary, Qazi et al. reported that EVE with reduced TAC missed noninferiority versus MMF with standard TAC based on BPAR rate[13]; thus, further consideration will be needed to yield any findings about safety for EVE with or without reducing TAC.

In this study, we also focused on vascular pathology according to the Banff classification. Positive ah and aah scores within 1 year of the EVE/TAC and MMF/TAC groups were not significantly different. Positive cv score within 1 year in the EVE/TAC and MMF/TAC groups was not significantly different either. EVE might have inhibitory effects on the proliferation of smooth muscle cell and neointima formation[14, 21]. Thus, longer observation is necessary.

The AEs observed in this study were oral aphthous ulcer and hyperlipidemia with the use of EVE. In contrast to an adult study[22], proteinuria was not increased after EVE treatment. In our EVE/TAC regimen, EVE starts 1 week after kidney transplantation; however, there was no wound healing problem.

Similarly as in previous reports, CMV infection rate with EVE/TAC was significantly lower than with MMF/TAC[23]. In Japan, valganciclovir (VGCV) started to prevail in commercial base in 2016. With the above background, a prophylactic dose of VGCV has been applied in our center since 2017. The prophylactic dose of this agent failed to decrease CMV infection at the present time. It can be emphasized that no CMV disease occurred with EVE/TAC.

EBV viremia and PTLD were more frequent in the EVE/TAC group, especially in EBV D+/R− recipients. One patient in the EVE/TAC group died because of disseminated intravascular coagulation due to PTLD over 1 year posttransplantation. She had severe oral aphtous ulcer, which might have complicated the disease. Tönshoff et al. also reported similar result for EBV viremia[12], and Franceschini et al. reported that EVE is a risk factor associated with EBV-DNA positivity in the univariate analysis[24]. In addition, some in vitro data showed a significant decrease in the activation of mTOR complex 1 downstream targets after treatment with EVE that is attenuated when combined with TAC and abolished the EVE-mediated EBV suppressive effects[25]. Therefore, it is assumed that EVE/TAC is not an effective EBV suppressant; we, therefore, observe patients with positive EBV PCR with caution.

Longitudinal growth, based on the change in height SD scores, was not affected by using EVE, similarly as in previous reports[12, 26].

In conclusion, this small-sample study found low CMV infection rate in the EVE group even with seronegative CMV from a seropositive donor. There was a similar trend toward better graft function without any severe acute rejection within a year. This novel immunosuppressant protocol in pediatric patients may be beneficial for maintaining longstanding graft function and catching up growth.

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