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Reduced Tacrolimus Trough Level Is Reflected by Estimated Glomerular Filtration Rate (eGFR) Changes in Stable Renal Transplantation Recipients: Results of the OPTIMUM Phase 3 Randomized Controlled Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Minimizing the tacrolimus dosage in patients with stable allograft function needs further investigation.


Material/Methods: We performed an open-label, randomized, controlled study from 2010 to 2016 in 7 tertiary teaching hospitals in Korea and enrolled 345 kidney transplant recipients with a stable graft status. The study group received reduced-dose tacrolimus, 1080–1440 mg/day of enteric-coated mycophenolate sodium (EC-MPS), and corticosteroids. The control group received the standard tacrolimus dosage and 540–720 mg/day of EC-MPS with steroids. The primary endpoint was the mean estimated glomerular filtration rate (eGFR) and change in the eGFR at 12 months after randomization.

Results: The mean tacrolimus trough level of the study group was 4.51 ± 1.62 ng/mL, which was lower than that of the control group, at 6.75 ± 2.82 ng/mL ($P < 0.001$). The primary endpoint was better in the study group in terms of change in eGFR ($P < 0.001$). The month 12 eGFRs were 73.6 ± 28.4 and 68.3 ± 18.1 mL/min/1.73 m² in the study and the control groups, respectively, but the difference did not reach statistical significance ($P = 0.07$). The incidence of adverse events was similar between the study and the control groups.

Conclusions: Minimizing tacrolimus to a trough level below 5 ng/mL combined with conventional EC-MPS can be considered in patients with a steady follow-up, as it was associated with small benefits in the changes of the eGFR (Clinicaltrials.gov number: NCT01159080).

MeSH Keywords: **Kidney Transplantation • Mycophenolic Acid • Tacrolimus**

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Background

Appropriate immunosuppression is a key component of successful organ transplantation. The aim of immunosuppressive medication is to prevent graft rejection while minimizing adverse events (AEs), including opportunistic infections. The search for the ideal immunosuppressive regimen is still underway and maintaining the balance between the drugs' adverse effects and their efficacy is an important and complex decision to be made by the clinicians and recipients [1].

In the kidney transplant era, calcineurin inhibitors (CNIs) have long been considered the main maintenance immune suppressive agent. CNIs are widely used in renal transplant recipients to prevent allograft rejection. Between cyclosporine and tacrolimus, the 2 widely used CNIs, evidence suggests that tacrolimus provides a better post-transplant prognosis, particularly in terms of allograft function [2–4]. However, long-term or higher doses of CNIs can also cause severe nephrotoxicity [5,6]. Therefore, many trials have investigated several strategies to minimize the dose of CNIs while keeping its benefits in preventing graft rejection [7–11]. Combining it with other immunosuppressants is a commonly practiced method, and many clinicians concomitantly use CNIs with corticosteroids and mycophenolate mofetil, which results in better post-transplant prognosis [12–14]. The recent development of enteric-coated mycophenolate sodium (EC-MPS) improved its well-known adverse effect, gastrointestinal symptoms [15,16], and several trials have investigated the outcome of reducing the tacrolimus dosage while adding EC-MPS [2,3].

In this randomized controlled trial, we minimized the dose of tacrolimus with the combined use of conventional-dose EC-MPS in patients who maintained stable allograft function in the 1 year post-transplant period. We set the target trough level of tacrolimus at <5 ng/mL, which, to the best of our knowledge, is the lowest dose ever tried. We aimed to determine whether such a reduced dose of tacrolimus, when combined with conventional EC-MPS use, could provide sufficient immunosuppression without a significant risk of AEs in low-risk stable patients.

Material and Methods

Study design

The OPTIMUM (Organ function Preservation by the combination treatment of the optimum dose of calcineurin inhibitor and mycophenolate sodium in kidney recipients) study was a multicenter, open-labeled, phase 4, randomized, controlled trial conducted at 7 centers in Korea between April 2010 and October 2016. The trial was conducted in accordance with the

Declaration of Helsinki. The independent Ethics Committees of each of the study hospitals reviewed and approved the study protocol before initiation. Written informed consent was provided by all participants before enrollment.

Study objective

The main objective of the study was to compare the efficacy and safety between the use of regular-dose tacrolimus with less EC-MPS and reduced-dose tacrolimus with conventional-dose EC-MPS in kidney transplant recipients. The main hypothesis was that reduced-dose tacrolimus with a conventional dose of EC-MPS would result in better post-transplant graft function than standard-dose tacrolimus with less EC-MPS.

Patient enrollment

Patients with ages of 20–75 years who received kidney transplantation 1–5 years before this study were screened for study enrollment. The other inclusion criteria were: 1) patients taking tacrolimus and maintenance corticosteroids, with or without an additional purine synthesis inhibitor within the last 3 months; 2) patients with a serum creatinine (sCr) level ≤ 2.0 mg/dL and variation of sCr <30% in the last 3 months; 3) patients with a urine proteinuria/creatinine ratio ≤ 1 g/g or 24-h urine protein ≤ 1 g/day in the most recent 3 months; and 4) patients who provided written informed consent.

The exclusion criteria were: 1) patients who received combined non-renal transplantation, multiple transplantation or re-transplantation; 2) whose graft was from a non-heart beating cadaveric donor, 3) human leukocyte antigen (HLA)-identical living related donor, or 4) ABO blood group-incompatible donor or HLA desensitized recipients; 5) patients with a history of sensitivity to mycophenolate sodium, mycophenolate acid, or mycophenolate mofetil, or to any other excipients; 6) patients with hypoxanthine-guanine phosphoribosyl transferase mutations; 7) patients with a history of disease that could affect absorption of the study medication (e.g., diabetic gastropathy or previous gastrectomy); 8) patients with positive serologic test results, in the recipient or donor, for human immunodeficiency virus or hepatitis B or C virus; 9) patients with liver function test abnormality (alanine aminotransferase, aspartate aminotransferase, or total bilirubin >3 times above the normal upper limit), neutropenia (absolute neutrophil count <1500/ μ L or white blood cell count <2500/ μ L), or thrombocytopenia (platelet count <75 000/ μ L); 10) patients with a history of cancer within the past 5 years, except for successfully treated localized non-melanocytic skin cancer; 11) patients who were either pregnant, lactating, or planning to become pregnant in the next 12 months; and 12) patients who had taken medicine for another trial within the past 30 days.

Intervention and follow-up

To ensure stability of the drug treatment and graft function before randomization, we implemented an additional 3-months run-in period. During this period, as screened patients were taking tacrolimus and corticosteroid with or without an additional purine synthesis inhibitor, they were switched to tacrolimus, corticosteroids, and EC-MPS before the study enrollment. Those who were already taking the regimen did not participate in the run-in period. The target tacrolimus trough blood level during the run-in period was not strictly controlled, as the period was before implementation of our intervention. Clinicians were encouraged to maintain the patients' level within 2–12 ng/mL during the run-in period, and for those who had too high or too low ranges of the tacrolimus trough level before study enrollment, randomization could have been postponed for more than 2 months. The patients who had severe laboratory abnormalities, aggravation of sCr or proteinuria, severe gastrointestinal disorder, discontinued study medication, or took other immunosuppressive agents for more than 2 days during the run-in period were classified as a screening failure and not included in the trial.

After the screening and run-in periods, patients were randomized via a web-based randomization program in a 1: 1 manner into the study group, which received a reduced dose of tacrolimus/conventional dose of EC-MPS, and the control group, which received a standard dose of tacrolimus/less dose of EC-MPS. In the study group, the target trough tacrolimus level was 2–5 ng/mL, and the dose of EC-MPS was 540–720 mg twice a day, whereas in the control group the target tacrolimus trough level was 5–10 ng/mL, and a lower dose of EC-MPS was taken (180–360 mg twice daily) [3,17]. Regarding maintenance corticosteroids, most of our study patients were treated with 500 mg of corticosteroid on the transplantation day, and the dose was rapidly tapered to 20 mg per day after 7 days from the transplant. According to patient status, additional tapering was done, and after 1 year from the operation, patients usually received 5 mg/day or 2.5 mg/day of corticosteroids for maintenance. During the entire study period starting from the initial screening, the minimum dose of corticosteroid was 2.5 mg of prednisolone (or the equivalent). The blood trough levels of tacrolimus were measured in each hospital's laboratory. Baseline characteristics were collected on randomization.

Study outcomes

After randomization, patients visited our clinics 4 times at intervals of 3 months. Visits within 2 weeks earlier or later than the set dates were considered acceptable. One month of additional follow-up was performed to identify AEs.

The primary endpoint was change in the estimated glomerular filtration rate (eGFR) from baseline to month 12, as calculated by the modification of diet in renal disease (MDRD) or Nankivell methods [18]. The co-primary endpoint was the absolute eGFR level, calculated by the MDRD equation at month 12 after randomization [19] and evaluated by the non-inferiority analysis. The secondary endpoint was analyzed at month 12 to compare the following efficacy outcomes: urine protein excretion, measured by assessing either 24-h collection of spot urine or the protein/creatinine ratio; number of performed allograft biopsies; treated or biopsy-proven acute rejection; discontinuation of intervention; and graft survival.

We evaluated safety primarily by collecting data on AEs, determined by clinical assessment including vital signs and laboratory examination measurements. Opportunistic infections, malignancies, other laboratory test abnormalities, and the calculated eGFR at each point were also investigated.

Statistical analyses

The predicted difference of the mean eGFR between the study and the control group was 8.3 ± 25 mL/min/1.73 m², which was derived from the study regarding the CNI dosage that had been published at the time our study design was conceived [20,21]. With a non-inferiority limit of 1.0 mL/min/1.73 m², 131 study participants in each group would result in a power of at least 90% with a one-sided type 1 error rate α of 2.5% [20]. Allowing for a 15% dropout rate and a 15% non-compliance rate, 350 patients, with 175 patients in each group, was the initial number of enrolled patients needed for the trial.

The primary endpoint, eGFR at month 12 after randomization, was compared using the non-inferiority analysis with a one-sided margin. The co-primary and the secondary outcomes, including change in the eGFR between baseline to month 12 and proteinuria, was assessed using the *t* test as well as other numerical variables. Categorical variables, including other secondary outcomes, were compared using Fisher's exact test. Continuous variables are expressed as mean (\pm standard deviation), as those variables showed normal distribution according to the Shapiro-Wilk's normality test, and categorical variables are shown as frequency (percentage). All AEs and severe adverse events (SAEs) are reported as frequencies in each group, and the total number of patients who experienced AEs and the number of total AEs between the study and the control groups was compared.

Among randomized patients, those who received allocated treatment at least once were included in the full analysis set (FAS). The per protocol (PP) set consisted of patients who ended the trial period on the allocated medication without discontinuing it. The FAS set was used to present the results, and

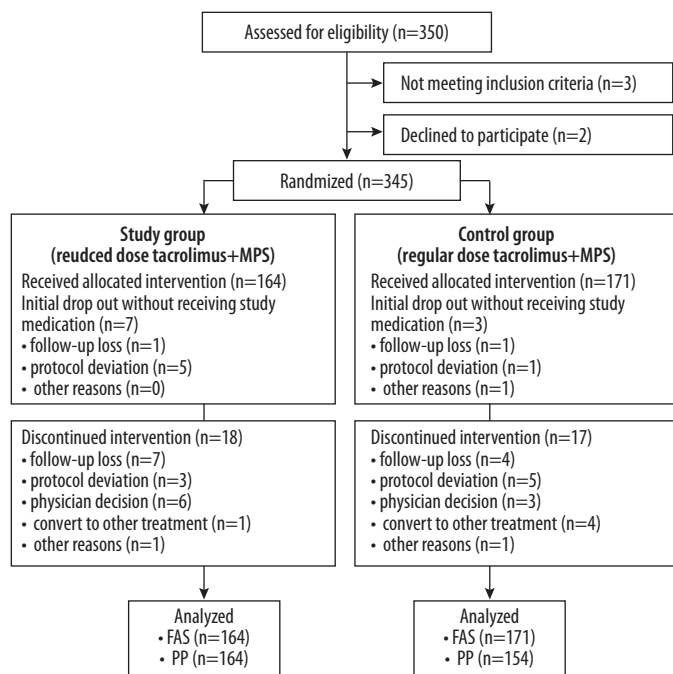


Figure 1. Study population. The flow diagram of the study population; MPS – mycophenolate sodium; FAS – full analysis set; PP – per protocol set.

the results of analysis of the PP set was not described unless significantly different.

All statistical analyses were performed using SPSS, version 23 (IBM, Armonk, NY). A statistical significance level of 0.05 was used.

Results

Study population

During the study period, the original targeted enrollment of 350 patients was successfully registered (Figure 1). Five patients failed the screening; therefore, 345 patients were randomized into the study and the control groups, and their median duration from transplant to randomization was 26 (16–40) months. Ten patients were not included in the FAS set because they initially dropped out of the study, so they did not receive the treatment even once and no data were available for them. As a result, 164 and 171 patients were included in the study and the control groups of the FAS set, respectively. Those who continued the initially allocated treatment until the end of the study were included in the PP set, and the numbers of patients were 146 in the study group and 154 in the control group.

Baseline characteristics

There was no significant difference in baseline characteristics between the study and the control groups in terms of

demographic, laboratory, and other clinical factors (Table 1). Most of the enrolled patients were already taking tacrolimus, a corticosteroid, and EC-MPS: 88.4% and 90.1% of the patients in the study and the control groups, respectively. Other patients were on tacrolimus, a corticosteroid, and mycophenolate mofetil, and no other regimen had been used in the study patients before enrollment.

Intervention

The study group received a significantly lower dose of tacrolimus ($P < 0.001$) and a higher dose of EC-MPS ($P < 0.001$) (Figure 2). The mean daily dosages of the corticosteroid were similar between the patient groups: 4.62 ± 1.30 mg in the study group and 4.61 ± 1.37 in the control group ($P = 0.94$). At the end of the run-in period, the study and the control groups had similar tacrolimus trough levels, and after randomization the trough level was significantly lower in the study group than in the control group ($P < 0.001$, Table 2). The proportion of patients who achieved the target concentration ranged from 55.7% to 76.0%, and the proportion was different only at the month 9 visit ($P = 0.004$). The mean tacrolimus trough level ranged from 4.51–4.63 ng/mL to 6.23–6.75 ng/mL in the study and the control groups.

Efficacy

At month 12, MDRD eGFRs were 73.2 ± 28.4 mL/min/1.73 m² and 68.3 ± 18.1 mL/min/1.73 m² in the study and the control

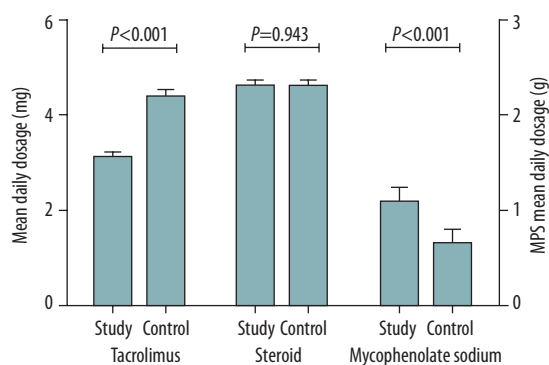
Table 1. Baseline characteristics of the study population.

	Study group (N=164)	Control group (N=171)	P Value
Age, years	43.4±10.4	44.7±10.7	0.27
Sex (male)	95 (57.9)	93 (54.4)	0.58
Height, cm	165.0±9.0	164.5±8.5	0.60
Body weight, kg	62.9±11.6	62.9±12.2	0.99
Serum creatinine, mg/dL	1.16±0.25	1.15±0.29	0.93
eGFR, mL/min/1.73 m ²			
by MDRD	68.7±15.5	68.6±17.2	0.96
by Nankivell	75.4±14.0	76.3±15.3	0.96
Urine protein excretion, g (24 h or spot urine-protein-creatinine-ratio)	0.17±0.52	0.14±0.34	0.49
Primary cause of ESRD			0.96
Diabetes	18 (11.0)	19 (11.)	
Hypertension	30 (18.3)	35 (20.5)	
IgA nephropathy	26 (15.9)	24 (14.0)	
Glomerulonephropathy other than IgA nephropathy	29 (17.7)	35 (20.5)	
Polycystic disease	5 (3.0)	6 (3.5)	
Nephrocalcinosis	4 (2.4)	1 (0.6)	
Obstructive disorder/reflux	2 (1.2)	1 (0.6)	
Pyelonephritis	1 (0.6)	1 (0.6)	
Other	7 (4.3)	6 (3.5)	
Unknown	42 (25.6)	43 (25.1)	
Previous RRT method			
Hemodialysis	105 (64.6)	118 (69.0)	
Peritoneal dialysis	23 (14.0)	28 (16.4)	
Not done	35 (21.3)	25 (14.6)	
Donor age	40.2±12.9	41.4±12.2	
Donor sex (male)	89 (54.6)	95 (56.9)	0.74
Donor source			0.41
Living-related	92 (56.1)	85 (49.7)	
Living-unrelated	38 (23.2)	41 (24.0)	
Deceased	34 (20.7)	45 (23.6)	
HLA mismatching			
HLA-A			0.35
0	32 (19.5)	22 (12.9)	
1	102 (62.2)	114 (66.7)	
2	28 (17.1)	34 (19.9)	
Not done	2 (1.2)	1 (0.6)	

Table 1 conitnued. Baseline characteristics of the study population.

	Study group (N=164)	Control group (N=171)	P Value
HLA-B			0.84
0	7 (4.3)	7 (4.1)	
1	93 (56.7)	99 (57.9)	
2	61 (37.2)	64 (37.4)	
Not done	3 (1.8)	1 (0.6)	
HLA-DR			0.59
0	14 (8.5)	20 (11.7)	
1	104 (63.4)	108 (63.2)	
2	43 (26.2)	42 (24.6)	
Not done	3 (1.8)	1 (0.6)	
Previous immunosuppressive agent use			0.73
Tacrolimus + steroid	0 (0.0)	0 (0.0)	
Tacrolimus + MPA + steroid	19 (11.6)	17 (9.9)	
Tacrolimus + Azathioprine + steroid	0 (0.0)	0 (0.0)	
Tacrolimus + EC-MPS + steroid	145 (88.4)	154 (90.1)	

Continuous variables are shown as mean (\pm standard deviation) values. Categorical variables are reported as number (%).

**Figure 2.** Mean daily dosage of the study medications.

Comparison of mean daily dosage of the study medications between the study and the control group. Left y-axis indicates the mean daily dosage of tacrolimus and steroid, the right y-axis shows the mean daily dosage of mycophenolate sodium.

groups, respectively, but the difference did not reach statistical significance ($P=0.07$) (Table 2). The eGFR of the study group was evidently non-inferior when compared to the eGFR of the control group ($P=0.01$). The co-primary outcome, change in

the eGFR, was significantly different between the subgroups, as both the percent and the absolute changes were better in the study group, regardless of which calculation method was used for GFR estimation (Figure 3).

Secondary end points were similar between the study group and the control group (Table 3). There was no graft failure or patient mortality during the study period. The urine protein levels at month 12 were 0.13 ± 0.16 g/g in the study group and 0.18 ± 0.33 g/g in the control group, which was not a significant difference ($P=0.10$). The incidence of acute rejection ($P=0.68$) and treatment failure ($P=0.31$) also showed a similar frequency in the study and the control groups.

Safety

There were 163 patients who had an AE during the trial, and among them, 32 patients experienced an SAE (Table 4). The overall incidence of AEs was similar between the study and the control groups. Clinically, 29 AEs and 2 SAEs in the study group and 33 AE sand 2 SAEs in the control group were assessed to be related to the study intervention. Four AEs in the study group and 3 AEs in the control group led to terminal discontinuation of the allocated treatment.

Table 2. Tacrolimus trough level, target concentration attainment, and eGFR during the study period.

	Study group (N=164)	Control group (N=171)	P Value
End of the run-in period, on randomization			
Tacrolimus trough level, ng/mL	5.69±2.03	5.62±1.92	0.76
eGFR, mL/min/1.73 m ²			
MDRD	69.6±16.3	69.3±18.0	0.88
Nankivell	76.0±14.7	76.4±16.4	0.60
Month 3 visit			
Tacrolimus trough level, ng/mL	4.59±1.67	6.09±2.13	< 0.001
Target concentration attainment, N (%)	88 (55.7)	97 (59.5)	0.50
eGFR, mL/min/1.73 m ²			
MDRD	71.2±16.4	69.5±17.0	0.36
Nankivell	78.0±15.4	77.1±16.0	0.80
Month 6 visit			
Tacrolimus trough level, ng/mL	4.60±1.67	6.23±2.02	< 0.001
Target concentration attainment, N (%)	93 (62.4)	108 (71.5)	0.11
eGFR, mL/min/1.73 m ²			
MDRD	71.1±16.9	69.6±17.2	0.43
Nankivell	77.8±15.9	77.5±15.9	0.64
Month 9 visit			
Tacrolimus trough level, ng/mL	4.63±1.74	6.29±1.75	< 0.001
Target concentration attainment, N (%)	84 (59.6)	111 (76.0)	0.004
eGFR, mL/min/1.73 m ²			
MDRD	72.3±18.4	69.4±17.0	0.16
Nankivell	79.2±17.3	77.4±15.7	0.87
Month 12 visit			
Tacrolimus trough level, ng/mL	4.51±1.62	6.75±2.82	< 0.001
Target concentration attainment, N (%)	89 (65.0)	106 (75.2)	0.07
eGFR, mL/min/1.73 m ²			
MDRD	73.2±28.4	68.3±18.1	0.07
Nankivell	79.9±22.3	76.3±15.9	0.12

Continuous variables are shown as mean (± standard deviation) values. Categorical variables are reported as number (%).

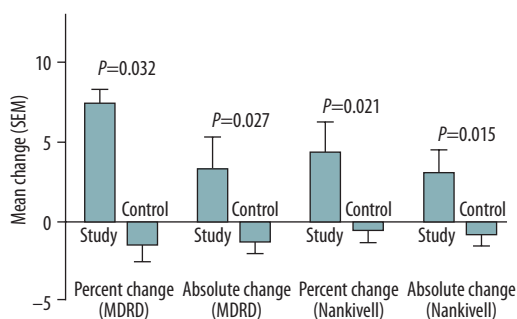


Figure 3. Change of eGFR from baseline to 12 months after randomization. Both percent (%) and absolute (mL/min/1.73 m²) changes of eGFR at 12 months after randomization are shown. The y-axis indicates the mean change and the error bars show the standard error of the mean. The study group had better outcome in terms of eGFR change according to all the methods we tested; SEM – standard error of the mean.

Table 3. Secondary efficacy endpoints.

	Study group (N=164)	Control group (N=171)	P value
Urine protein/creatinine ratio (g/g)	0.13±0.16	0.18±0.33	0.10
Graft loss, N (%)	0 (0)	0 (0)	>0.999
Number of kidney biopsy, N (%)	4 (2.4)	3 (1.8)	0.72
Treated or biopsy proven acute rejection, N (%)	3 (1.8)	2 (1.2)	0.68
Intervention discontinuation, N (%)	18 (10.9)	17 (9.9)	0.76

Continuous variables are shown as mean (\pm standard deviation) values. Categorical variables are reported as number (%).

Table 4. Number of patients experienced adverse events.

	Study group (N=164)	Control group (N=171)	P value
Number of patients experienced SAE	14 (8.5)	18 (10.5)	0.58
Mean SAE per patient	0.10±0.36	0.13±0.42	0.47
Number of patients experienced AE	77 (47.0)	86 (50.3)	0.59
Mean AE per patient	1.17±1.71	1.15±1.50	0.92
General manifestation	4 (2.4)	8 (4.7)	0.38
Blood or lymphatic disorder	1 (0.6)	0 (0.0)	0.49
Cardiac disorder	1 (0.6)	7 (4.1)	0.07
Vascular	4 (2.4)	1 (0.6)	0.21
Gastrointestinal disorder	27 (16.5)	28 (16.4)	> 0.999
Hepatobiliary disorder	0 (0.0)	1 (0.6)	> 0.999
Respiratory disorder	14 (8.5)	15 (8.8)	> 0.999
Infection or inflammation	32 (19.5)	37 (21.6)	0.69
Ear and labyrinth disorder	1 (0.6)	1 (0.6)	> 0.999
Eye disorder	2 (1.2)	1 (0.6)	0.62
Endocrine disorder	3 (1.8)	7 (4.1)	0.34
Laboratory abnormality	4 (2.4)	4 (2.3)	> 0.999
Musculoskeletal disorder	12 (7.3)	18 (10.5)	0.34
Renal and urinary disorder	7 (4.3)	5 (2.9)	0.57
Nervous system	8 (4.9)	11 (6.4)	0.64
Skin and subcutaneous tissue	10 (6.1)	4 (2.3)	0.11
Neoplasm	1 (0.6)	1 (0.6)	> 0.999
Psychiatric illness	3 (1.8)	1 (0.6)	0.36
Injury	1 (0.6)	0 (0.0)	0.49
Reproductive system	2 (1.2)	3 (1.8)	> 0.999

Continuous variables are shown as mean (\pm standard deviation) values. Categorical variables are reported as number (%).

The most commonly identified AE according to body system was infection or inflammation, and the gastrointestinal system was the site of the second most prevalent AEs. The most common infection and inflammatory disorder was upper respiratory tract infection, which occurred in 29 patients in the study group and 31 patients in the control group. Opportunistic infection was mainly caused by herpes zoster, and 6 patients in each group developed the infection. BK nephropathy was identified in 1 patient of each group. Regarding gastrointestinal disorders, the general distribution of AEs was similar, including diarrhea, abdominal discomfort, and epigastric discomfort. There was only 1 case of malignancy in the study population; 1 patient in the study group was diagnosed as having bladder cancer. Overall absolute eGFR values were not significantly different at each time point (Table 2).

Discussion

Our study revealed that the tacrolimus dosage could be reduced to a trough level as low as <5 ng/mL in kidney transplant recipients with stable renal function. When using the combination of tacrolimus, corticosteroids, and EC-MPS for maintenance immunotherapy, reducing the tacrolimus dosage while using the conventional dose of EC-MPS showed a non-inferior outcome when compared with standard-dose tacrolimus with a less dose of EC-MPS. Furthermore, reduced use of tacrolimus might show a beneficial outcome in terms of change in the eGFR, without a significant increase in the incidence of major AEs.

CNIs in addition to other immunosuppressive medication have been established as the standard maintenance immunosuppressive strategy for kidney transplant recipients [9]. Among CNIs, tacrolimus was associated with better renal function than cyclosporine [4,22–24]. Moreover, reducing the dose of CNIs has been considered beneficial for renal allograft function [7–11,25]. Nonetheless, the trough level of tacrolimus in previous studies was still higher than the target level of the current study [21,26]. Two recent trials demonstrating the similar beneficial effect of reduced-dose tacrolimus and combined use of EC-MPS also had either higher trough levels [2] or the trough level of the study reached about 5 ng/mL by the end of the study [3]. Therefore, our study, with a longer follow-up duration and a consistently low mean trough level, further showed that even tacrolimus trough levels as low as 4–5 ng/mL, when combined with the conventional dose of EC-MPS, can be safely used without a significant increase in graft rejection. A similar research question was asked in a previous study [11], and the beneficial effect of a minimal dose of tacrolimus was suggested. However, direct comparison of allograft function between the low-dose and the standard-dose tacrolimus groups was not performed in the study. Taken together

with the evidence showing the beneficial effect of reduced-dose tacrolimus [3,11], such a regimen could be recommended in some patients rather than discontinuation of the medication, since CNI withdrawal resulted in an increased risk of acute rejection [9,27–29].

The original study protocol suggested that the target trough tacrolimus level should be within the 2–5 ng/mL range. A large proportion of patients reached the target during the study period; however, the mean tacrolimus trough level at each time point was near the upper limit of the target, and most patients had a trough level of 4–5 ng/mL. There was a large overlap of trough levels between the study group and the control group, which was similar to the result of a previous study [11]. This might reflect that many clinicians still hesitated to minimize the tacrolimus dosage. Also, the narrow target range might have contributed to the proportion of patients who failed to achieve the target tacrolimus concentration. An additional trial could target even lower mean trough levels in order to investigate the optimal tacrolimus dose range; however, possible clinician reluctance in minimizing tacrolimus dose should be considered during such a study.

The overall incidence of acute rejection, even clinically diagnosed events, was lower when compared with other studies with a similar follow-up duration [2,7,21,25,26]. One of the main reasons for the result might be that we included patients who were in the remote period after renal transplantation and had successfully maintained their graft function for a certain period. Therefore, the study population could be considered as a low-risk patient group. In addition, differences in ethnicity might have some influence [30,31], as all patients were East Asian and from a single nation. Further study is warranted to reveal whether such low tacrolimus doses could be used in different races.

One of the most common adverse effects of mycophenolate mofetil when co-administrated with tacrolimus is gastrointestinal symptoms, and other AEs have been reported [16,32]. However, with a conventional dose of EC-MPS, no significant change in AEs was observed in comparison with a lower dosage. This might be because we used EC-MPS, which is known to subjectively improve patients' symptoms [15]. Similar studies using EC-MPS also showed that a dose of 720 mg twice a day was generally well tolerated [2,3]. Although the total incidence of AEs was higher with 1440 mg/day of EC-MPS used in a previous study [3], the study was limited by the small number of patients ($n < 50$) in each group, and the frequency of EC-MPS-related AEs remained unchanged. Therefore, based on the results of our study, a dose of 720 mg twice a day of EC-MPS, which is now commonly considered as the usual dosage, could be a good strategy to maintain an effective immunosuppressive effect when using a reduced tacrolimus dose.

Our study has several limitations. First, the clinical trial was performed on a single ethnic group, as mentioned above. An additional study is needed to confirm whether the result could be applied to different populations. Second, some study participants failed to maintain their target trough tacrolimus level. The overall difference was small, and a large overlap of trough levels existed. However, the mean trough level was still significantly different, and even this small difference in trough level was associated with a beneficial effect on post-transplant allograft function. Third, information on peri-transplantation immunosuppression, including induction therapy such as anti-thymoglobulin antibody or basiliximab, was not included in our study, and the induction therapy was administered according to each hospital's protocol. However, although some difference might have existed in immunosuppressive induction between the centers, the effect of remote immunosuppression might not have had a large impact on the study results. Fourth, as our study enrolled patients who had their transplantation more than 1 year before and retained stabilized allograft function for a certain period, the study group should be considered as a low-risk group. In addition, protocol-based biopsy was unavailable, as stable patients would be reluctant to provide informed consent and performing the procedure without a definite clinical benefit would be an unethical. Therefore, application of our study results should be limited to those low-risk patients, and whether such low-dose tacrolimus could provide sufficient immunosuppression for moderate- to high-risk patients needs further validation. Lastly, the donor-specific antibody or anti-HLA antibodies was not measured in the current study. This was mainly because

measuring donor-specific anti-HLA antibodies using a single antigen Luminex assay was not available in Korea when the study was planned because of an insurance issue. Investigating donor-specific antibody production in the post-transplant period would further show whether sufficient immune suppression is provided to patients with a reduced dose of immunosuppressive agents.

Conclusions

Minimizing the tacrolimus dosage to a trough level as low as 4–5 ng/mL showed a small beneficial effect on change in the eGFR in patients with relatively stable post-transplant kidney function, when used with conventional-dose EC-MPS. Conventional doses of EC-MPS did not increase AEs when compared with lower dosages, and they provided sufficient adjunct immunosuppression when used with a reduced dose of tacrolimus. Such a tacrolimus reduction strategy could be considered in kidney transplant recipients with relatively stable allograft function.

Statement

The funding source had no role in study design, data collection, monitoring, or conduct of the study.

Conflicts of interest

None.

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