日本人腎移植患者のミコフェノール酸モフェチル投与量に及ぼす体重の影響

Implications of clinical mycophenolate mofetil dose according to individual body weight in Japanese renal transplant recipients

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HIGHLIGHTS

・Body weight affects the MPA AUC:MMF dose ratio.

・We need to consider individual body weight when deciding the MMF dose.

・The MMF dose:body weight ratios can be index to predict MPA AUC without therapeutic drug monitoring.

・A MMF dose:body weight ratio of 10–16 mg/kg predict MPA AUC between 30 and 60 μg·h/mL with a probability of approximately 75%.

ABSTRACT

Background: Mycophenolic mofetil (MMF) is generally administered at a fixed dose of 0.5–1.5 g/day without considering individual body weight (BW) in Japanese renal transplant outpatients receiving maintenance therapy. We aimed to investigate the implications of the area under the curve of mycophenolic acid (MPA AUC):MMF dose ratio by individual BW and suggest the index of MMF dose according to individual BW.

Methods: Forty-three Japanese patients who received a renal transplant at least 6 months prior to the study were enrolled. Blood samples were collected at four time points: at predose, 20 min, 1 h, and 3 h after MMF administration.

Results: The mean ± standard deviation MMF dose, MPA AUC, and BW of all patients were 581 ± 207 mg/day, 36.2 ± 18.7 μg·h/mL, and 56.3 ± 11.1 kg, respectively. Patients with lower BW tended to have a higher MPA AUC:MMF dose ratio than patients with higher BW. There was a significant correlation between the MMF dose:BW ratios and MPA AUC (r^2 = 0.330; P < 0.01). The rate of MPA AUC between 30 and 60 μg·h/mL with the MMF dose:BW ratio of 10–16 mg/kg was 73.7%.

Conclusion: Individual BW appears to affect the MPA AUC:MMF dose ratio; therefore, we need to consider individual BW when deciding on a MMF dose. The MMF dose:BW ratio of 10–16 mg/kg could predict MPA AUC between 30 and 60 μg·h/mL with a probability of approximately 75%.

Therefore, it could be a useful index for outpatients, as it is difficult to withdraw blood frequently from such patients.

KEYWORDS

Renal transplantation, mycophenolic acid, maintenance therapy, body weight, the mycophenolate mofetil dose:body weight ratios

INTRODUCTION

Mycophenolate mofetil (MMF) is an inactive prodrug used in maintenance immunosuppressive therapy for patients after renal transplantation (1-3). After oral administration, MMF is extensively absorbed and hydrolyzed to its active metabolite mycophenolic acid (MPA) by serum esterases in the stomach and small intestine (4, 5). MPA acts as an uncompetitive and reversible inhibitor of inosine-5'-monophosphate dehydrogenase, an enzyme necessary for lymphocyte mitosis (6), and is metabolized to its inactive metabolite MPA-phenyl-glucuronide (MPAG) by uridine diphosphate glucuronosyltransferase in the kidney and liver (4). However, MPAG is reverted to MPA by bacterial β-glucuronidase in the gut lumen, reflected by a secondary plasma peak of MPA approximately 8–12 h after MMF administration (7).

Although many studies have investigated the correlation between the trough MPA level or other single concentration–time levels and clinical effect, several have found a poor correlation (8-10) because there is wide inter- and intrapatient variability in MPA pharmacokinetics with exposures varying ten-fold (11, 12). Masatomo *et al.* (13) reported that monitoring of the trough level is insufficient for therapeutic drug monitoring. Therefore, the area under the curve (AUC) of MPA (MPA AUC) is used as an index for therapeutic drug monitoring (14, 15). Its suggested target range is between 30 and 60 μg·h/mL (14-16), because there is a significant relationship between

MPA AUC and the risk of acute rejection (8, 17). Le Meur *et al*. reported that the concentration-controlled group had fewer treatment failure episodes than the fixed-dose group (29.2% vs. 47.7%, respectively), and biopsy-proven acute rejection was significantly lower in the concentration-controlled group (7.7% vs. 24.6%, respectively) (18). Although MPA AUC is primarily estimated using the trapezoidal rule, measuring the full profile over 12 h is challenging because of cost, time efficiency, and patient discomfort. Therefore, limited sampling strategies (LSSs), which use MPA concentration at several blood sampling time points, have been developed. Reportedly, LSS using three blood sampling points at 20 min, 1 h, and 3 h or at predose, 2 h, and 4 h after MMF administration accurately reflected MPA AUC (19, 20). It was also reported that LSS using blood sampling at 2 h, 4 h, and 9 h is a reliable and accurate method to estimate MPA AUC because the 9 h blood sample contains important information on the secondary plasma peak of MPA (20, 21). Bruchet *et al*. systematically reviewed and assessed the quality of numerous studies pertaining to LSSs (22).

MMF is initially administered at a dose of 2–3 g/day after renal transplantation and then reduced depending on individual immunosuppressive status or adverse effects such as diarrhea or cytomegalovirus infection (23). In Japanese patients receiving maintenance therapy a few months after renal transplantation, MMF is generally administered at a fixed dose of 0.5–1.5 g/day without

therapeutic drug monitoring, because LSS requiring at least three blood sampling time points, especially at 9 h, is difficult to achieve in outpatients in clinical practice and facilities measuring MPA concentrations are limited. However, it remains controversial whether Japanese patients should receive approximately the same MMF fixed dose as European patients with a greater body weight (BW). In addition, it was recently reported that estimated reduction of the dose for Asian, including Japanese renal transplant patients, was approximately 20%–46% to reach the same target range for Caucasians (24). In fact, many patients, especially with lower BW developed adverse effects at a dose of 500 mg/day or 750 mg/day in our hospital and, consequently, received a lower MMF dose. However, in Japanese patients, few reports describe the measurement of MPA AUC under maintenance therapy and the relationship between the MMF dose and MPA AUC is still unknown. In addition, it has not been investigated how individual BW affects the MPA AUC:MMF dose ratio.

Therefore, the aim of this study was to investigate the implications of the MPA AUC:MMF dose ratio by individual BW and suggest an index of MMF dose according to individual BW in Japanese renal transplant outpatients receiving maintenance therapy.

MATERIALS AND METHODS

Study population and design

We enrolled outpatients who underwent renal transplantation more than 6 months prior to this study. The study protocol was approved by the Ethics Committee of Ryukyu University Hospital, Okinawa, Japan, and written informed consent was obtained from each patient.

Immediately after renal transplantation, all patients received combination immunosuppressive therapy comprising 2 g/day of MMF (CellCept®; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) and 0.15–0.3 mg/kg of the calcineurin inhibitor tacrolimus (Prograf®; Astellas Pharma Inc., Tokyo, Japan) at the designated times of 09:00 and 21:00, and 40 mg of the steroid methylprednisolone (Medrol®; Pfizer Japan Inc., Tokyo, Japan) at 09:00. The dose of each medicine was subsequently reduced according to the individual's immunosuppressive status. During this study, the MMF dose remained unchanged for at least 1 month.

Sample collection and analytical methods

A 4-mL blood sample was withdrawn from each patient at the following four time points: predose, 20 min, 1 h, and 3 h after oral MMF administration. Plasma was isolated by centrifugation at 3000 × *g* for 10 min, and stored at −80°C until analysis.

Standard MPA was purchased from Shiguma (St. Louis, MO) and all other reagents and chemicals were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). A stock solution of MPA (2 mg/mL) in methanol was prepared and further diluted to obtain solutions of

different concentrations (100 and 10 μg/m). We added 20 μL of oxazepam solution (40 μg/mL) as an internal standard and 400 μL of methanol to 200 μL of plasma. After mixing for 30 sec, the solutions were centrifuged at 13000 × *g* for 5 min. The clear supernatant (80 μL) was passed through a syringe filter (0.45 μm, Millex-LH, Japan) and 20 μL was injected into a chromatography column (Shim-Pack CLC-Phenyl; Shimadzu Corporation, Kyoto, Japan) with an internal diameter of 150 × 4.6 mm. The mobile phase consisted of methanol/0.05 mol/L sodium phosphate buffer (46/54 v/v) containing acetyltrimethylammonium bromide (100 mg/L w/v) and triethanolamine (0.25% v/v, adjusted to pH 2.5 with phosphoric acid). The pump flow rate of the mobile phase was 0.5 mL/min, the column temperature was set at 30°C, and the wavelength of the ultraviolet radiation detector was set at 251 nm.

MPA plasma concentrations were measured using high-performance liquid chromatography. MPA AUC was calculated by the following LSS using three MPA concentrations sampled at 20 min, 1 h, and 3 h after MMF administration (19):

$$\text{MPA AUC} = 0.58 \times C_{20\ \text{min}} + 0.97 \times C_{1\ \text{h}} + 6.64 \times C_{3\ \text{h}} + 3.48$$

($r^2 = 0.946$). Statistical analyses were performed with the statistical software statcel 3. A *P* value of <0.05 was considered statistically significant.

RESULTS

Forty-three Japanese patients (19 men, 24 women) were enrolled in this study. The characteristics of these patients are shown in Table 1. The mean ± standard deviation (SD) age and time since initiation of MMF administration were 52.6 ± 11.1 and 4.9 ± 3.0 years, respectively. All patients had stable renal and liver function.

The mean ± SD MMF dose of all patients was 581 ± 207 mg/day (658 ± 246 mg/day for men, 521 ± 143 mg/day for women). There was a significant difference in mean ± SD MMF dose between men and women. Five patients received 1000 mg/day, nine received 750 mg/day, 24 (over half) received 500 mg/day, and five received 250 mg/day. The pharmacokinetics parameters at each MMF dose are shown in Table 2. The mean ± SD MPA AUC of all patients was 36.2 ± 18.7 μg·h/mL (37.5 ± 19.9 μg·h/mL for men, 35.1 ± 17.6 μg·h/mL for women). There was no significant difference in mean ± SD MPA AUC between men and women. The mean ± SD MPA AUC values at each MMF dose were 51.3 ± 24.0 μg·h/mL at 1000 mg/day, 50.1 ± 22.4 μg·h/mL at 750 mg/day, 30.1 ± 10.5 μg·h/mL at 500 mg/day, and 25.3 ± 11.0 μg·h/mL at 250 mg/day. There was a significant correlation between MMF dose and MPA AUC (r^2 = 0.247, P < 0.01), and MPA AUC decreased as MMF dose decreased (Fig. 1A). Seventeen patients (39.5%) had MPA AUC of <30 μg·h/mL, 23 (53.5%) had MPA AUC between 30 and 60 μg·h/mL, and three (7%) had MPA AUC of ≥60 μg·h/mL. Three patients (60%) at 1000 mg/day, six (67%) at 750 mg/day, 12 (50%) at 500

mg/day, and two (40%) at 250 mg/day had MPA AUC between 30 and 60 μg·h/mL. In contrast, the mean ± SD BW of all patients was 56.3 ± 11.1 kg (61.4 ± 11.9 kg for men, 52.2 ± 8.4 kg for women). There was a significant difference in mean ± SD BW between men and women. The mean ± SD BW at each MMF dose were 71.5 ± 16.4 kg at 1000 mg/day, 56.1 ± 7.4 kg at 750 mg/day, 55.0 ± 8.4 kg at 500 mg/day, and 47.4 ± 5.9 kg at 250 mg/day. Thus, MMF dose decreased as BW decreased, and consequently, five patients receiving 250 mg/day had much lower BW (Fig. 1B).

The correlation between BW and MPA AUC:MMF dose ratio are shown in Fig. 2. Patients with a lower BW tended to have a higher MPA AUC:MMF dose ratio and there was a significant correlation between them ($r^2 = 0.140$, $P < 0.05$). MMF dose and the pharmacokinetics parameters of MPA AUC, MPA AUC:MMF dose ratio and oral clearance in three groups with BW of <50, 50–60, and ≥60 kg are shown in Table 3. The mean MMF dose increased as BW increased; however, the mean MPA AUC did not change. The mean MPA AUC:MMF dose ratio of patients with BW of <50 kg was the highest in the three groups and tended to decrease as BW increased. In contrast, the mean oral clearance tended to increase as BW increased.

The mean ± SD MMF dose:BW ratios of all patients were 10.4 ± 3.3 mg/kg (10.7 ± 3.6 mg/kg for men, 10.1 ± 2.9 mg/kg for women). There was no significant difference in the MMF dose:BW ratios between men and women. In contrast, there was a significant correlation between

the MMF dose:BW ratios and MPA AUC (r^2 = 0.330, P < 0.01) (Fig. 3). In three groups with the MMF dose:BW ratios of <10, 10–16, and ≥16 mg/kg, MPA AUC was between 30 and 60 μg·h/mL in 33.3%, 73.7%, and 66.7%, respectively (Fig. 4).

DISCUSSION

All patients at our hospital initially received MMF at a dose of 2 g/day with tacrolimus and methylprednisolone immediately after renal transplantation. MMF dose was subsequently reduced by 250 mg/day depending on the individual's immunosuppressive status and administrated at a fixed dose of 1000 mg/day. If adverse events occurred, the MMF dose was reduced further. Among the 43 patients in this study, several experienced adverse effects, such as leucopenia, diarrhea, or infections with cytomegalovirus or zoster virus. These adverse effects were ameliorated by reducing MMF dose. Finally, 24 patients received 500 mg/day and five received 250 mg/day. The mean BW of patients receiving 500 mg/day and 250 mg/day was 55.0 kg and 47.4 kg, respectively, and the mean BW of these patients was much lower than patients receiving 1000 mg/day. As shown in Fig. 1B and Table 3, patients with a lower BW tended to receive a lower dose of MMF. These results indicate that the MMF dose of patients with lower BW was reduced more than that of patients with higher BW because an MMF dose of 750 mg/day or 1000 mg/day could cause adverse events. Therefore, the mean MMF dose was 658 mg/day and 521 mg/day for men

and women with a mean BW of 61.4 kg and 52.2 kg, respectively, demonstrating significant differences in mean BW and MMF dose between men and women.

In contrast, as the result of measurement of MPA concentrations, the mean ± SD MPA AUC of all patients was 36.2 ± 18.7 μg·h/mL, 53.5% of all patients had MPA AUC between 30 and 60 μg·h/mL, and MPA AUC decreased as MMF dose decreased as with BW. However, as shown in Fig. 2 and Table 3, patients with lower BW tended to have a higher MPA AUC:MMF dose ratio. In three groups with BW of <50, 50–60, and ≥60 kg, the MPA AUC:MMF dose ratio of the group with BW of <50 kg was the highest. This indicates that patients with lower BW could have higher MPA AUC than patients with higher BW at the same MMF dose and MPA AUC:MMF dose ratio could be affected by individual BW. In patients receiving 500 mg/day and 250 mg/day, the rates between 30 and 60 μg·h/mL of MPA AUC were high at 50% and 40%, respectively. In the studies of Le Guellec et al. and Staatz et al. (25, 26), a trend toward increased MPA clearance with higher BW was observed, providing evidence to support the fact that BW did influence MPA pharmacokinetics. Our study also demonstrated that oral clearance of patients with BW of ≥60 kg was 21.1 L/h, higher than that of patients with a BW of <50 kg.

As shown in Fig. 3, there was a significant correlation between the MMF dose:BW ratios and MPA AUC (r^2 = 0.330, P < 0.01), indicating that MPA AUC could be predicted by the MMF

dose:BW ratios. In three groups with the MMF dose:BW ratios of <10, 10–16, and ≥16 mg/kg, the rate of MPA AUC between 30 and 60 μg·h/mL of the group of 10–16 mg/kg was 73.7% and the highest of all groups. In contrast, 60% and 67% of patients receiving 1000 mg/day and 750 mg/day of MMF, respectively, also had MPA AUC between 30 and 60 μg·h/mL. However, the mean BW of these patients was 71.5 kg and 56.1 kg, respectively, which did not significantly deviate from the average Japanese BW. If the BW of these patients was extremely high or low, MPA AUC could deviate from the 30 and 60 μg·h/mL range. MPA AUC of the patient with the highest BW at 100 kg in all patients was 28.6 μg·h/mL, but low at the MMF dose of 1000 mg/day, and that of the patient with the lowest BW at 36.2 kg was 37.0 μg·h/mL, but high at 250 mg/day. Kaplan *et al*. (27) reported that the fixed dosing of MMF might not be optimal for patients with a BW of <50 kg and >100 kg, as the heaviest patients would require more and the lightest patients would require less MMF. Therefore, our study suggests that the MMF dose:BW ratio is a useful index to predict MPA AUC without therapeutic drug monitoring and an MMF dose:BW ratio of 10–16 mg/kg is approximately 75% likely to predict MPA AUC between 30 and 60 μg·h/mL in outpatients receiving maintenance therapy.

This study has a few limitations. First, we calculated MPA AUC from LSS using MPA concentration at three time points of 20 min, 1 h, and 3 h after MMF administration because this

was the best estimated correlation model for adult patients receiving maintenance therapy more than 6 months after renal transplantation (19). However, there were differences in study design among the many reports on LSSs (22). Although the trapezoidal rule is considered the most accurate method to calculate MPA AUC from MPA concentrations derived from blood sampling at several time points, this methods requires that patients stay at the hospital and involves a great deal of stress, and therefore, it is considered to be difficult in clinical practice. Second, this survey was performed at a single center and involved a small number of participants. Further validation of the predictive value of the MMF dose:BW ratio in a larger number of patients is necessary.

CONCLUSIONS

We measured MPA concentrations and calculated MPA AUC of 43 Japanese outpatients more than 6 months after renal transplantation. The study demonstrated that Japanese patients with lower BW tended to have a higher MPA AUC:MMF dose ratio, indicating that the MPA AUC:MMF dose ratio could be affected by individual BW. Therefore, we suggest that we need to consider individual BW when deciding on the MMF dose. In addition, a significant correlation between the MMF dose:BW ratios and MPA AUC was detected and it was demonstrated that an MMF dose:BW ratio of 10–16 mg/kg were approximately 75% likely to predict MPA AUC between 30 and 60 μg·h/mL. Therefore, our findings suggest that the MMF dose:BW ratio is useful to predict MPA

AUC without therapeutic drug monitoring and an MMF dose:BW ratio of 10–16 mg/kg could be a useful index for outpatients receiving maintenance therapy, as it is difficult to withdraw blood frequently from such patients.

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FIGURE LEGENDS

Fig. 1. Correlation between mycophenolate mofetil dose and (A) the area under the curve of mycophenolic acid ($r^2 = 0.247$; $P < 0.01$) and (B) body weight ($r^2 = 0.245$; $P < 0.01$)

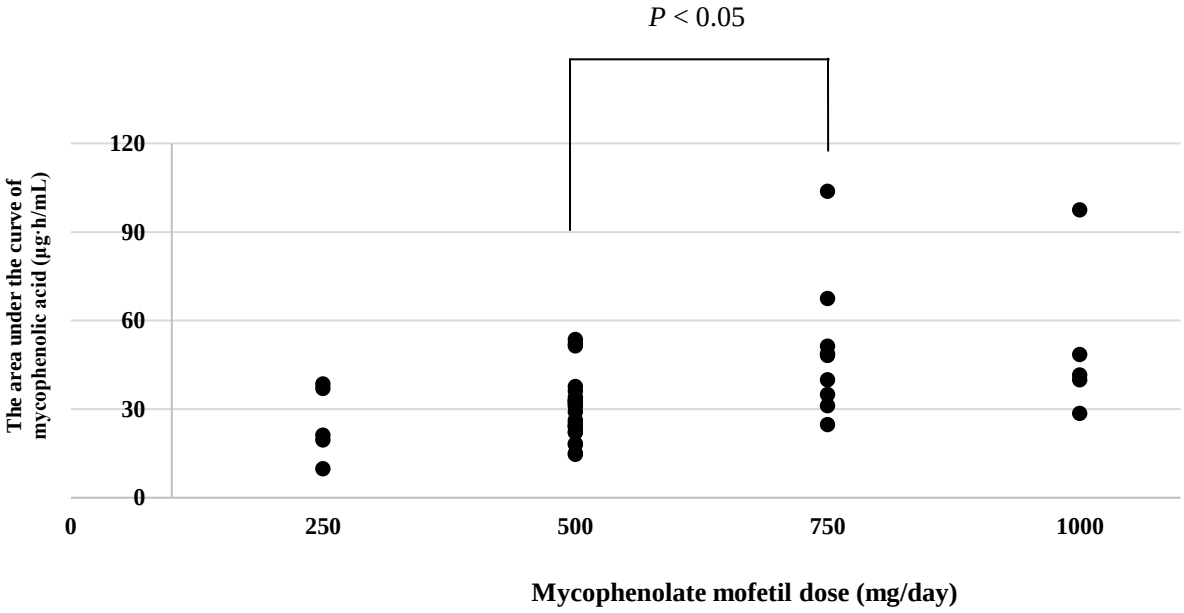
Fig. 2. Correlations between the area under the curve of mycophenolic acid:mycophenolate mofetil dose ratio and body weight ($r^2 = 0.140$; $P < 0.05$)

Fig. 3. Correlations between the area under the curve of mycophenolic acid and mycophenolate mofetil dose:body weight ratios (the area under the curve of mycophenolic acid = 3.297 × mycophenolate mofetil dose:body weight ratio + 2.010; $r^2 = 0.330$, $P < 0.01$)

Fig. 4. The percent of the tertile of the area under the curve of mycophenolic acid in each of three groups classified according to mycophenolate mofetil dose:body weight ratios

Fig. 1.

A


P < 0.05
The area under the curve of mycophenolic acid (μg·h/mL)
120
90
60
30
0
0
250
500
750
1000
Mycophenolate mofetil dose (mg/day)

B

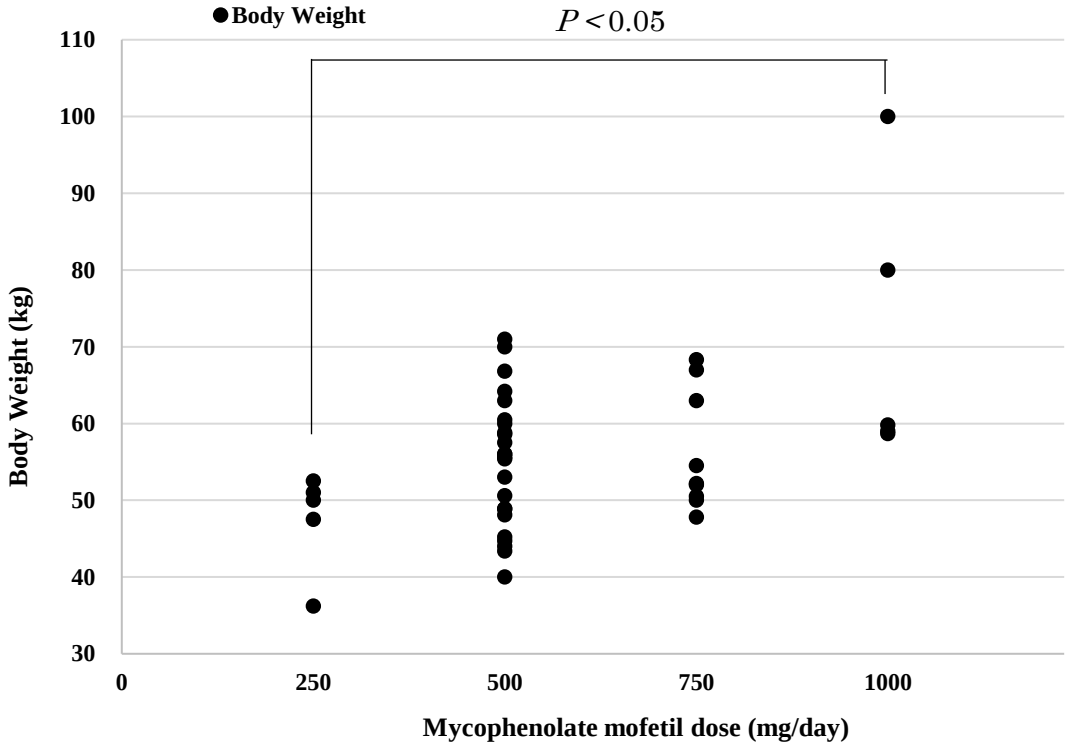

Body Weight
P < 0.05
Body Weight (kg)
110
100
90
80
70
60
50
40
30
0
250
500
750
1000
Mycophenolate mofetil dose (mg/day)

Fig. 2.

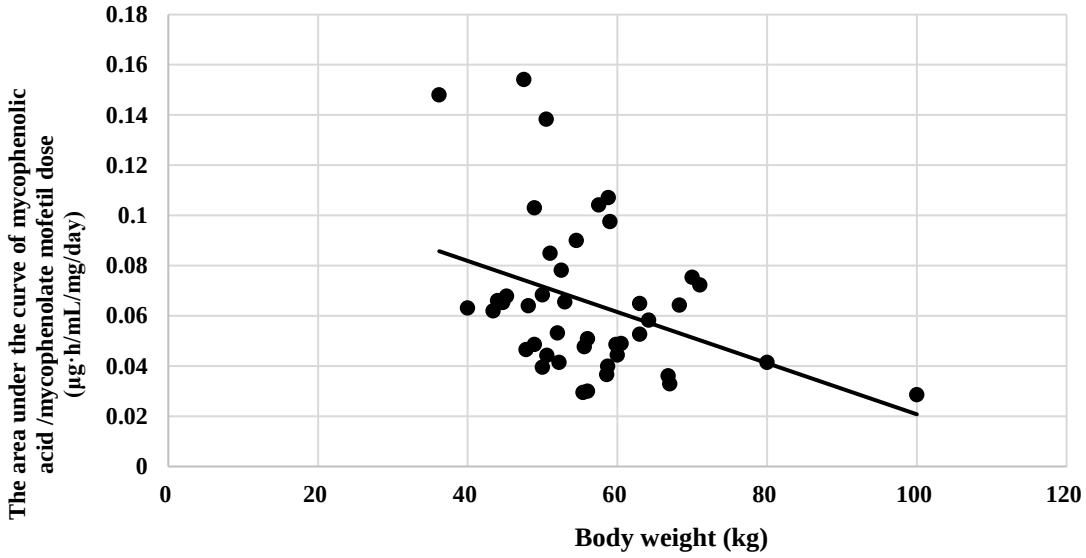

The area under the curve of mycophenolic acid /mycophenolate mofetil dose (μg·h/mL/mg/day)
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
20
40
60
80
100
120
Body weight (kg)

Fig.3.

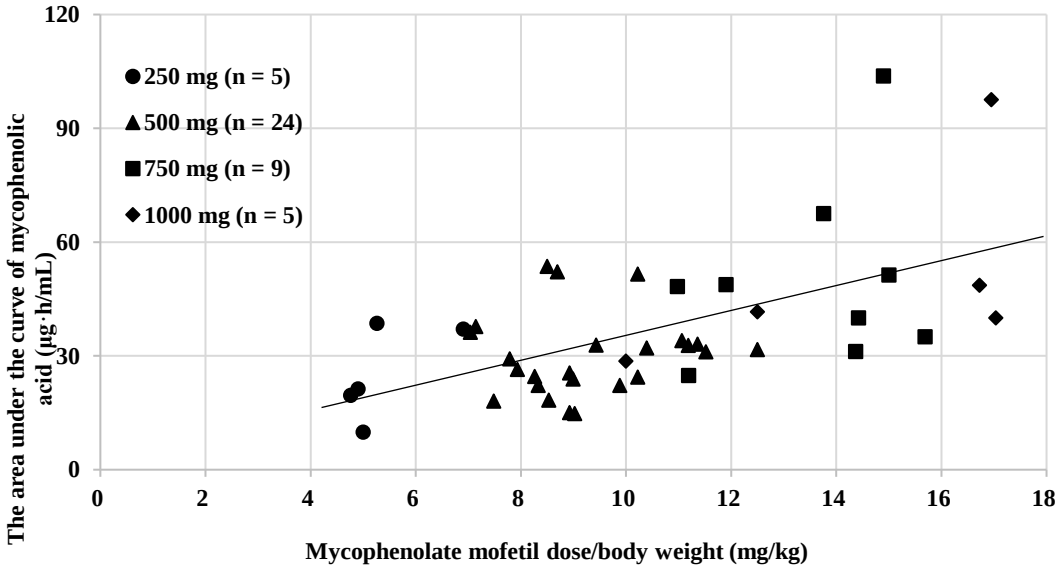

120
90
60
30
0
0
2
4
6
8
10
12
14
16
18
250 mg (n = 5)
500 mg (n = 24)
750 mg (n = 9)
1000 mg (n = 5)
The area under the curve of mycophenolic acid (μg·h/mL)
Mycophenolate mofetil dose/body weight (mg/kg)

Fig. 4.

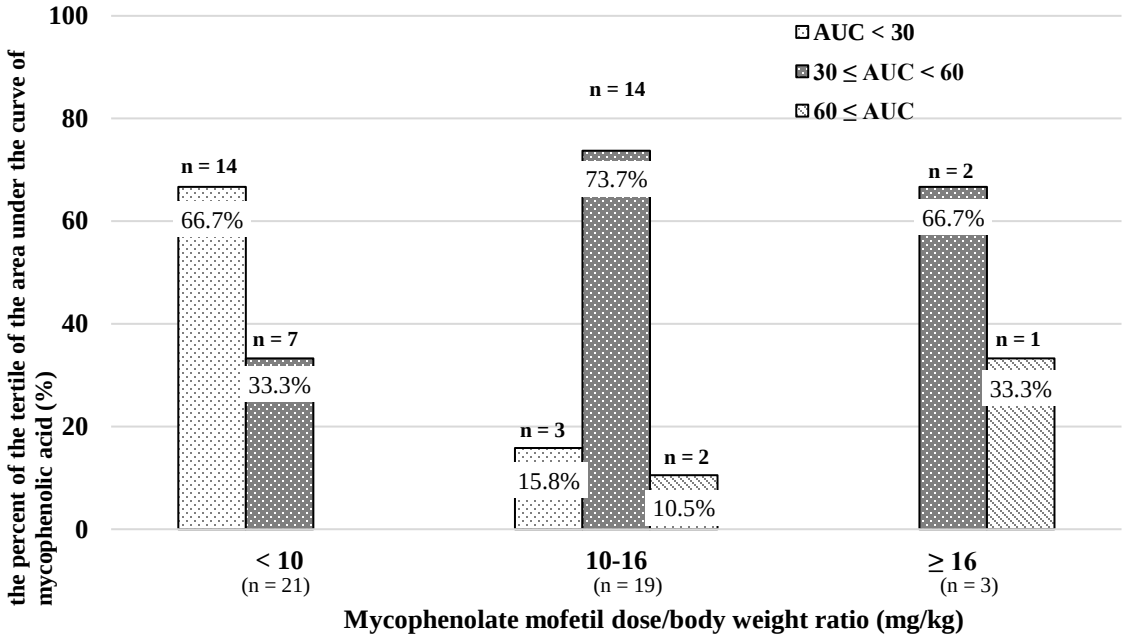

100
80
60
40
20
0
the percent of the tertile of the area under the curve of mycophenolic acid (%)
AUC < 30
30 ≤ AUC < 60
60 ≤ AUC
n = 14
66.7%
n = 7
33.3%
n = 14
73.7%
n = 3
15.8%
n = 2
10.5%
n = 2
66.7%
n = 1
33.3%
< 10
(n = 21)
10-16
(n = 19)
≥ 16
(n = 3)
Mycophenolate mofetil dose/body weight ratio (mg/kg)

Table 1.		
No. patients	43	
Age (years)	52.6 ± 11.1	(33–78)
Sex		
Men	19	
Women	24	
Body weight (kg)	56.3 ± 11.1	(36–100)
Men	61.4 ± 11.9	
Women	52.2 ± 8.4	
Donor type (living: cadaver)	27: 16	
Blood type (identical: compatible)	35: 8	
Time since initiation of MMF administration (years)	4.9 ± 3.0	(0.58–14.8)
Serum creatinine (mg/dL)	1.1 ± 0.4	(0.6–2.3)
Serum GOT (U/L)	19.1 ± 5.4	(9–34)
Serum GPT (U/L)	17.1 ± 9.6	(6–59)
Concomitant medication		
Tacrolimus (calcineurin inhibitor)		
Dose (mg/day)	3.0 ± 1.5	(1.0–6.0)
Trough Levels (ng/mL)	6.7 ± 2.0	(3.6–11.6)
Methylprednisolone (steroid)		
Dose (mg/day)	3.4 ± 1.7	(0.0–8.0)

Data are presented as numbers or means ± standard deviation (range).

Characteristics of patients who underwent renal transplantation

Table 2.

	250 mg/day (n = 5)	500 mg/day (n = 24)	750 mg/day (n = 9)	1000 mg/day (n = 5)	All patients (n = 43)
Body weight (kg)	47.4 ± 5.9	55.0 ± 8.4	56.1 ± 7.4	71.5 ± 16.4	56.3 ± 11.1
MMF dose:body weight (mg/kg)	5.4 ± 0.8	9.3 ± 1.5	13.6 ± 1.7	14.6 ± 2.9	10.4 ± 3.3
MPA AUC (μg·h/mL)	25.3 ± 11.0	30.1 ± 10.5	50.1 ± 22.4	51.3 ± 24.0	36.2 ± 18.7
MPA AUC:MMF dose (μg·h/mL/mg)	0.101 ± 0.044	0.060 ± 0.021	0.067 ± 0.030	0.051 ± 0.024	0.065 ± 0.030
Oral clearance (L/h)	12.6 ± 6.8	18.7 ± 6.5	17.6 ± 6.6	23.0 ± 8.0	18.2 ± 7.2

Data are presented as means ± standard deviation

Body weight and the pharmacokinetics parameters according to the MMF dose class

The mean body weight, the MMF dose:body weight ratio, and MPA AUC at 1000 mg/day were the highest and decreased as MMF dose decreased.

Table 3.

	<50 kg (n =11) (44.9 ± 3.8)	50-60 kg (n = 20) (54.5 ± 3.3)	≥60 kg (n = 12) (69.4 ± 10.5)	All patients (n = 43) (56.3 ± 11.1)
MMF dose (mg)	477 ±128	600 ± 229	645 ± 189	581 ± 207
MPA AUC (μg·h/mL)	34.6 ±6.3	39.4 ± 25.4	32.1 ± 9.7	36.2 ± 18.7
MPA AUC:MMF dose (μg·h/mL/mg)	0.080 ± 0.035	0.064 ± 0.029	0.051 ± 0.014	0.065 ± 0.030
Oral clearance (L/h)	14.3 ± 4.65	18.6 ± 7.73	21.1 ± 6.63	18.2 ± 7.2

Data are presented as means ± standard deviation

MMF dose and the pharmacokinetics parameters according to the body weight class

The mean MMF dose value with body weight (BW) <50 kg was the lowest among the three groups and tended to increase with BW. However, the mean MPA AUC among the three groups was not significantly different. The mean MPA AUC:MMF dose ratio decreased and oral clearance increased as BW increased, indicating that the rate of MPA AUC increase varied by BW.