A Study of the Pharmacokinetic Comparison between the Generic and Original Form of Mycophenolate Mofetil Among Thai Renal Transplant Patients

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ABSTRACT

Background. Mycophenolic acid (MPA) is one of the main immunosuppressive regimens used after kidney transplantation (KT). The less expensive, generic form of mycophenolate mofetil (MMF) (Immucept®) is recently available in Thailand. Comparisons of the pharmacokinetic profiles between the original and generic forms of MMF among post-KT patients are limited.

Methods. This prospective cohort study recruited KT patients receiving stable doses of MMF 1000 mg daily along with tacrolimus and steroids. All participants were prescribed CellCept® 500 mg every 12 hours for at least 2 weeks before measuring the MPA area under the curve from 0 to 12 hours ($AUC_{0\text{-}12}$). CellCept® was switched to Immucept® 500 mg every 12 hours for 2 weeks and MPA $AUC_{0\text{-}12}$ was remeasured.

Results. Twenty patients with a median follow-up time of 35.4 (11.13–198.83) months were enrolled. Mean MPA $AUC_{0\text{-}12}$ of Immucept® was higher than CellCept® without statistical significance (48.27 ± 2.31 μg•hr/mL vs 42.19 ± 15.20 μg•hr/mL; P value = .59). No difference was revealed regarding the minimum measured concentration, maximum measured concentration, and time point with maximum concentration between both drugs. While on CellCept®, 5 patients (25%) had an MPA $AUC_{0\text{-}12} < 30.0$ μg•hr/mL, but 3 patients (15%) had MPA $AUC_{0\text{-}12} < 30.0$ μg•hr/mL when receiving Immucept®. However, 3 (15%) and 6 (30%) patients had MPA $AUC_{0\text{-}12} > 60.0$ μg•hr./mL when treated with CellCept® and Immucept®, respectively.

Conclusion. Generic MMF exhibited a comparable pharmacodynamic profile as the original formulation. MPA $AUC_{0\text{-}12}$ was more than 30.0 μg•hr/mL among most patients receiving MMF 1000 mg/day.

MYCOPHENOLATE has been one of the main immunosuppressive regimens after kidney transplant (KT) for a long time. Several studies and meta-analyses have shown the superiority of mycophenolate over azathioprine in reducing acute rejection and rate of allograft loss [1–3]. The adequacy of mycophenolate exposure can be evaluated by measuring the area under the curve (AUC) from 0 to 12 hours ($AUC_{0\text{-}12}$) of mycophenolic acid (MPA), an active metabolite, after administering mycophenolate. One related study demonstrated that an $AUC_{0\text{-}12}$ from 30.0 to 60.0 μg•hr/mL was associated with a reduced risk of acute rejection and drug toxicity [4].

This work was supported by funding from The Kidney Foundation of Thailand Grant and the Thai Transplantation Society.

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0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.03.063

The current recommended total daily dosage ranges between 2 and 3 g of mycophenolate mofetil (MMF) [1]. However, the appropriate dosage to achieve a target $AUC_{0\text{-}12}$ among Thai patients is lower than that in western populations [5–7]. Our previous study showed that more than half of patients receiving MMF 1 g daily had $AUC_{0\text{-}12} > 30.0$ μg·hr/mL [5]. Despite the lower dosage requirement among our patients, the cost of immunosuppression is still high in developing countries, including Thailand.

The first less expensive, generic form of MMF (Immucept®; Intas Pharmaceuticals Ltd, Ahmedabad, India) has recently become available in Thailand. The standard guidelines recommend use of generic drugs that are bioequivalent to the original formulations [1]. Studies among healthy subjects have proven the bioequivalence of Immucept to an original drug, CellCept® (Genentech, San Francisco, CA, United States). Prescribing generic immunosuppressive agents for KT recipients in our country constitutes a new issue, and several physicians are concerned with the potentially inferior quality of generic drugs, which may lead to allograft rejection. Studies comparing pharmacokinetic (PK) parameters between generic and original drug forms among KT recipients, generally receiving MMF along with tacrolimus and steroids, are lacking. Thus, this study was conducted to compare PK profiles, especially MPA $AUC_{0\text{-}12}$, that impact transplant outcomes between CellCept® and Immucept® among our stable KT patients.

MATERIAL AND METHODS

We conducted an investigator-initiated, prospective crossover study. The research protocol was approved by the Siriraj Institutional Review Board, and the study was conducted according to the Declaration of Helsinki principles. Participants consisted of 20 patients underwent KT at least 1 year prior and who had estimated glomerular filtration rates > 30.0 mL/min/1.73m^2. All patients received mycophenolate at a daily dosage equivalent to MMF 1000 mg along with tacrolimus and prednisolone, without any change in the dosage for 3 months. Any participants who had active infection, pregnancy, history of rejection, serious gastrointestinal adverse events, and noncompliance were excluded.

After patients gave informed consent, baseline demographic data were collected. The enrolled patients continued on CellCept® or received a conversion from enteric-coated mycophenolate sodium (Myfortic®) 360 mg every 12 hours to CellCept® 500 mg every 12 hours for at least 2 weeks. The first MPA $AUC_{0\text{-}12}$ was measured before and after a CellCept® 500 mg tablet (containing 500 mg of MMF) was given. Whereupon CellCept was switched to Immucept® 500 mg every 12 hours for 2 weeks, another MPA $AUC_{0\text{-}12}$ was evaluated after Immucept® 500 mg (2 capsules containing 250 mg of MMF) was prescribed.

The MPA $AUC_{0\text{-}12}$ was calculated from blood MPA level at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after MMF exposure. The MPA level was measured using the mean of ultraperformance liquid chromatography and photo diode array (Waters Corporation, Milford, MA, United States).

Baseline characteristics and demographic data were summarized as percentage or mean and standard deviation for normally distributed data or median with interquartile ranges for others. Categorical variables were compared using the χ^2 test. Continuous variables were compared using the Student *t* test or Mann-Whitney *U* test. Comparison of PK profiles between CellCept® and Immucept® was determined by a paired *t* test. Pearson's correlation analysis was used to find the correlation between each MPA level and MPA $AUC_{0\text{-}12}$. All statistical analyses were executed using SPSS, Version 17.0 (Chicago, IL, United States).

RESULTS

Of the 20 patients with a median time after KT of 35.40 (12–198.80) months, 10 patients (50%) received living donor KT. Mean estimated glomerular filtration rates was 77.7 ± 18.9 mL/min/1.73m^2. All patients received tacrolimus with a mean trough level of 5.41 ± 1.13 μg/L and prednisolone with median daily dose of **5.0** (2.5–5.0) mg. Baseline demographic data are summarized in Table 1.

Mean MPA $AUC_{0\text{-}12}$ after prescribing Immucept® tended to be higher than CellCept®, but without statistical significance (48.27 ± 20.31 μg·hr/mL vs 42.19 ± 15.20 μg·hr/mL; $P = .06$). No difference was found in trough concentration, maximum measured concentration (Cmax), or the time point with the maximum concentration. All pharmacologic profiles are summarized in Table 2. The MPA levels at each time interval were similar for the 2 formulations, except at 1 hour after exposure, in which the MPA level while receiving Immucept® was significantly higher than CellCept® (14.86 ± 7.16 μg/mL vs 10.73 ± 6.44 μg/mL; $P = .024$) (Fig 1).

Because of the higher trend in MPA $AUC_{0\text{-}12}$ while receiving the generic form, the bioequivalence analysis of

Table 1. Baseline Demographic Data of All Enrolled Participants Who Received CellCept® Dosage 500 mg Twice Daily and Subsequently Switched to Immucept® at the Same Dosage

Characteristics	Value
Age, mean ± SD, y	46.5 ± 12.1
Time post kidney transplant, median (IQR), mo	58.27 (11.13–198.83)
Female, No. (%)	13 (65)
Living donor KT, No. (%)	10 (50)
HLA mismatch, median (IQR)	2 (0–4)
Body weight, median (IQR), kg	62.48 (43.5–99.0)
Height, median (IQR), cm	160 (137–172)
Body mass index, median (IQR), kg/m^2	24.64 (18.34–34.26)
Serum creatinine, mean ± SD, mg/dL	1.0 ± 0.25
Estimated GFR, mean ± SD, mL/min/1.73m^2	77.7 ± 18.9
Hemoglobin, mean ± SD, g/dL	13.6 (10.9 ± 15.7)
WBC count, median (IQR), /mm^3	7.320 (4.040–12,400)
Serum albumin, mean ± SD, g/dL	4.38 ± 0.25
Concomitant use of omeprazole, No. (%)	2 (10)
Tacrolimus trough level, mean ± SD, μg/mL	5.38 ± 1.11
Daily tacrolimus dosage, median (IQR), mg	2.0 (1.0–6.0) mg
Daily prednisolone dosage, median (IQR), mg	5.0 (2.5–5.0)
Previous use of EC-MPS, No. (%)	15 (75)

Abbreviations: EC-MPS, enteric coated mycophenolate sodium; GFR, glomerular filtration rate; IQR, interquartile range; KT, kidney transplantation; SD, standard deviation; WBC, white blood cell.

Table 2. The Pharmacokinetic Profile Compared Between CellCept® and Immucept®

	CellCept®	Immucept®	*P* Value
$AUC_{0\text{-}12}$, μg·hr/mL	42.19 ± 15.20	48.27 ± 20.31	.06
Cmin, μg/mL	1.00 ± 0.60	1.04 ± 0.74	.68
Cmax, μg/mL	18.53 ± 10.93	20.96 ± 10.28	.22
C0, μg/mL	2.14 ± 1.24	2.00 ± 1.58	.64
Tmax, hours	1.00 (0.5–2.0)	1.00 (0.5–4.0)	.79

Values are reported either as mean ± standard deviation or as median (interquartile range).

Abbreviations: $AUC_{0\text{-}12}$, area under the curve from 0 to 12 hours; C0, trough concentration; Cmax, maximum measured concentration; Cmin, minimum measured concentration; Tmax, the time point with the maximum concentration.

MPA $AUC_{0\text{-}12}$ was performed using WinNonlin Software, Version 8.0 (Certara Inc, NJ, United States). The mean ratios and the 90% confidence interval of ln-transformed MPA $AUC_{0\text{-}t}$ was 103.11% (100.28% to 105.94%), which was within the acceptable limit. Because the graph of MPA levels at each time for all patients was quite similar in the pattern, we could develop a practical model for MPA $AUC_{0\text{-}12}$ prediction using Pearson's correlation analysis. Our model estimated MPA $AUC_{0\text{-}12}$ from MPA concentrations as

$$\text{MPA } AUC_{0\text{-}12} = -0.251 + 3.64(C0) + 0.82(C0.5) + 1.978(C1.5) + 3.801(C4)$$

where C0, C0.5, C1.5, and C4 are the concentrations at 0, 0.5, 1.5, and 4 hours. This model had a cofficient of determination (r^2) of 0.954 and a standard error of estimation of 4.88 μg·hr/mL.

MPA $AUC_{0\text{-}12}$ was in the target range of 30.0 to 60.0 μg·hr/mL in 12 (60%) and 11 (55%) of patients after prescribing CellCept® and Immucept®, respectively. An MPA $AUC_{0\text{-}12} > 60.0$ μg·hr/mL was found in 3 patients (15%) while on CellCept® and 6 patients® (30%) who received Immucept®. On the other hand, 5 (25%) and 3 (15%) of patients had an MPA $AUC_{0\text{-}12} < 30.0$ μg·hr/mL after taking CellCept® and Immucept®, respectively. Patients who had a subtherapeutic MPA $AUC_{0\text{-}12}$ while on original MMF had higher weight (74.62 ± 15.09 kg vs 58.44 ± 14.13 kg, $P = .043$) and height (166.0 ± 5.7 cm vs 154.7 ± 9.1 cm, $P = .009$).

Regarding adverse effects, 1 patient developed a maculopapular rash at all extremities on the fifth day after beginning of Immucept®, which subsided after treating with an oral antihistamine without discontinuation of the study drug. No gastrointestinal, hematologic, or other adverse events were found. The allograft function remained stable during the study without any acute rejection.

DISCUSSION

KT is the best way to improve survival and quality of life among most patients with end-stage renal disease; however, the cost of immunosuppression remains high, especially in developing countries. In an effort to reduce drug-related expenses, generic substitutes have been used in several countries, including developed countries. One recent report from the United States showed that the proportion of dispensed generic MMF was high, up to 90% of overall patients receiving MMF after KT [8].

The use of generic immunosuppressants among KT recipients has been debated because many immunosuppressive agents have a narrow therapeutic index. However, MMF has a wide therapeutic window, so concern about an inadvertent low or high drug level might not be as great as in

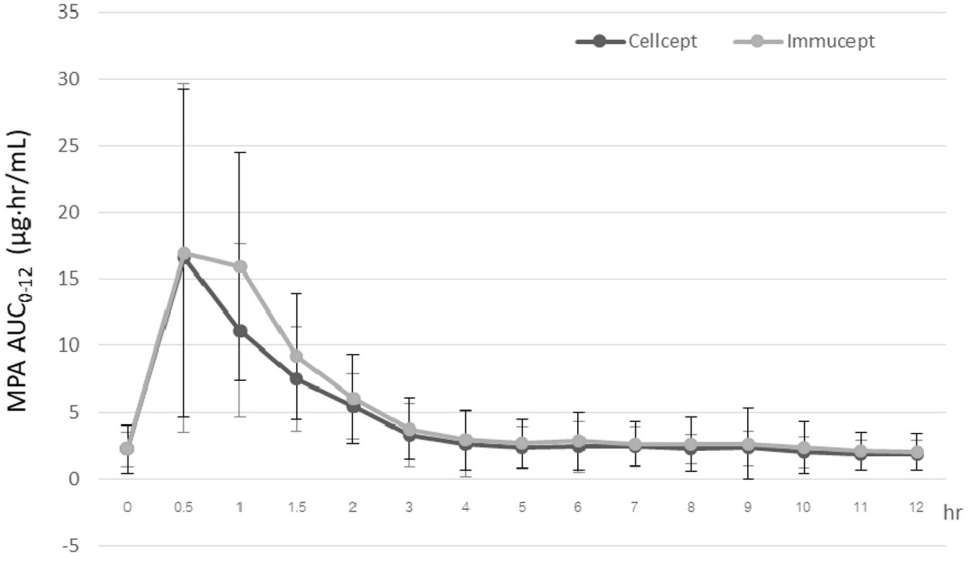

Fig 1. Mean plasma MPA concentrations obtained after 500-mg dose administration of CellCept® and Immucept®. Plasma MPA level at 1 hour after exposure was significantly higher while receiving Immucept®. $AUC_{0\text{-}12}$, area under the curve from 0 to 12 hours; MPA, mycophenolic acid

calcineurin inhibitors. Therapeutic level monitoring for MMF is not recommended for all KT patients, but when needed, evaluating MPA $AUC_{0\text{-}12}$, which has been proven to be associated with allograft outcome, is suggested [4]. However, assessing MPA $AUC_{0\text{-}12}$ in clinical settings is sophisticated, and the use of abbreviated models to predict MPA $AUC_{0\text{-}12}$ is more feasible. Our study also developed an abbreviated model, which correlated excellently to AUC, and we began to use this equation to estimate AUC among our patients.

Several related studies regarding the bioequivalence of original vs generic MMF among healthy volunteers showed comparable PK profiles, including MPA $AUC_{0\text{-}12}$, Cmax, and the time point with maximum concentration, between the 2 formulations, according to FDA requirement [9–12]. Pooled results from a recent meta-analysis also revealed the bioequivalence between original and generic MMF [13]; however, the risk of detection and publication bias is high. Sunder-Plassmann et al [14] performed a comparative PK study between Myfenax® and the original formulation involving stable KT recipients and found that AUC was within an acceptable range but Cmax was significantly lower. The difference in Cmax might have limited clinical value as long as the AUCs are comparable. Despite the dissimilarity in PK patterns between enteric coated mycophenolate sodium and MMF, pharmacologic actions and clinical outcomes are comparable because they provided similar AUCs. Our study showed similarity in pivotal PK profiles and bioequivalence in MPA $AUC_{0\text{-}12}$ between original and generic forms [15]. This might encourage the use of generic MMF with a bioequivalency standard in our society to decrease costs.

Our study confirmed previous findings that Thai populations required lower doses of MMF to achieve appropriate MPA $AUC_{0\text{-}12}$. Most patients (75% and 85% when receiving CellCept® and Immucept® 1000 mg daily, respectively) had MPA $AUC_{0\text{-}12} > 30.0$ μg·hr/mL [5]. The reason that Asian populations could maintain adequate AUC with lower MMF doses may be from lower weight and genetic differences in UGT2B7 involved in MMF metabolism [5].

Our study had some limitations because we did not perform a full bioequivalence analysis, used different forms of drugs (capsules for Immucept® and tablets for CellCept®), and used too short a duration of study to assess the hard outcomes. However, we performed our study among KT recipients, which should better represent real clinical settings in which patients have regular and concomitant use of multiple immunosuppressive drugs.

CONCLUSION

Generic MMF demonstrated a comparable PK profile as original formulation. MPA $AUC_{0\text{-}12}$ was more than 30.0 μg·hr/mL in most patients receiving MMF 500 mg twice daily. A model using limited time points of MPA level to predict MPA $AUC_{0\text{-}12}$ of MMF might be applied for therapeutic MPA monitoring in clinical practice.

ACKNOWLEDGMENTS

We wish to thank all the patients for their cooperation and participation in this study and Ms. Patcharaporn Manopinives for help in the bioequivalence analysis.

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