

ARTICLE

Pharmacokinetics and pharmacodynamics profiles of enteric-coated mycophenolate sodium in female patients with difficult-to-treat lupus nephritis

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Abstract

Relapsed or resistant lupus nephritis (LN) is considered a difficult-to-treat type of LN, and enteric-coated mycophenolate sodium (EC-MPS) has been used in this condition. Therapeutic drug monitoring using the area under the plasma mycophenolic acid concentration from 0 to 12 h postdose (MPA-AUC_{0-12h}) $\geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ is a useful approach to achieve the highest efficiency. This study assessed EC-MPS's pharmacokinetic (PK) and pharmacodynamic (PD) profiles and investigated an optimal level of the single time point of plasma MPA concentration. Nineteen biopsy-proven patients with class III/IV LN received 1440 mg/day of EC-MPS for 24 weeks. PK (maximum plasma MPA concentration [C_{max}], time to C_{max} , and MPA-AUC_{0-12h}) and PD (activity of inosine-5'-monophosphate dehydrogenase [IMPDH]) parameters were measured at weeks 2, 8, 16, and 24. We found that IMPDH activity decreased from baseline by 31–42% within 2–4 h after dosing, coinciding with the increased plasma MPA concentration. MPA-AUC_{0-12h} $\geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ was best predicted by a single time point MPA concentration at C0.5, C2, C3, C4, and C8 ($r^2 = 0.516, 0.514, 0.540, 0.611, \text{ and } 0.719$, respectively), independent of dose, albumin, urine protein/creatinine ratio, and urinalysis. The MPA-C0.5 cutoff of 2.03 g/ml yielded the highest overall sensitivity of 85% and specificity of 88.2% in predicting MPA-AUC_{0-12h} $\geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$. A single timepoint of plasma MPA-C0.5 $\geq 2.03 \mu\text{g}/\text{ml}$ may help guide EC-MPS adjustment to achieve adequate drug exposure. Further study of EC-MPS used to validate this cutoff is warranted.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Therapeutic drug monitoring (TDM) is crucial in lupus nephritis (LN) treated with mycophenolic acid (MPA), especially mycophenolate mofetil. The area under the plasma concentration-time curve of MPA from time 0 to 12 h

(MPA-AUC_{0-12h}) $\geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ or a single plasma MPA concentration (C0 or C1) are used as tools to enhance the highest treatment efficacy. In addition, enteric-coated mycophenolate sodium (EC-MPS) was also used to treat relapsed or resistant LN. However, little is known regarding the TDM of EC-MPS.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study assessed EC-MPS's pharmacokinetics (PKs) and pharmacodynamics (PDs) in adult patients with relapsed or resistant LN and investigated a surrogate single timepoint of plasma MPA concentration with optimum plasma level cutoff as an alternative for MPA-AUC.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study provided EC-MPS's PK and PD profiles and suggested a surrogate single timepoint of plasma MPA concentration with optimum plasma level cutoff as potential alternatives for MPA-AUC₀₋₁₂ $\geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ to be applied in TDM.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study supports the role of TDM in relapsed or resistant LN treated with EC-MPS. In addition, a single timepoint of plasma MPA concentration at C0.5 with the proposed cutoff at $\geq 2.03 \mu\text{g}/\text{ml}$ is a TDM tool that can be easily applied in clinical practice. However, a more significant number of study patients is required.

INTRODUCTION

Lupus nephritis (LN) is one of the most severe organ manifestations of systemic lupus erythematosus (SLE), presenting in 30–50% of Asian patients and is associated with substantial morbidity and mortality.¹ Despite advances in the treatment regimen for LN, ~35% of patients may relapse, and 5–20% progress to end-stage renal disease. Hence, treatment modality for relapsed or resistant LN is still challenging globally.²

Mycophenolate is a standard immunosuppressive treatment for LN. It is recommended for participants with relapsed or resistant proliferative LN.¹ Mycophenolate mofetil (MMF) and enteric-coated mycophenolic acid (EC-MPS) are two types of mycophenolate used clinically to treat active LN in both induction and maintenance phases.³ MMF and EC-MPS are prodrugs that must be converted to active mycophenolic acid (MPA) by plasma esterase after gastrointestinal absorption. MPA acts as a noncompetitive, selective, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an enzyme responsible for the de novo pathway of lymphocytes.³

Many studies reported pharmacokinetic (PK) profiles of MMF in LN.⁴⁻¹² However, less evidence was shown for EC-MPS.^{5,13} Studies also reported pharmacodynamic (PD) properties of MMF, represented by IMPDH activity, in childhood-onset SLE,¹⁴ kidney,^{15,16} and liver transplantation,¹⁷ but no study directly examines plasma EC-MPS concentration and IMPDH activity in relapsed or resistant LN.

Our group has previously shown that variations in PK profiles of MPA were associated with treatment outcomes in LN,^{5,9} and the area under the plasma concentration-time curve of MPA from time 0 to 12h (MPA-AUC_{0-12h}) of $\geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ was used as a target AUC⁵ together with plasma MPA concentration at 1-h postdose (C1) as a predictor of clinical response⁶ in those patient groups. However, MPA-AUC_{0-12h} is time-consuming compared to a single timepoint of plasma concentration measurement. Therefore, trough plasma MPA concentration (C0) is also used for therapeutic drug monitoring (TDM) of MMF. However, this may not be directly applied to EC-MPS as there are differences in the PK properties of both types of mycophenolate.^{5,13,18} It will benefit those difficult-to-treat patients with LN on treatment with EC-MPS if any other blood sampling timepoint can also be used as a surrogate for TDM and predicts the target MPA-AUC.

This study assessed the PKs and PDs of EC-MPS in adult patients with relapsed or resistant LN and investigated a surrogate single timepoint of plasma MPA concentration with optimum plasma level cutoff as an alternative for MPA-AUC.

METHODS

This study used stored data of the main study entitled – A multicenter, randomized controlled study of enteric-coated mycophenolate sodium for the treatment of relapsed or resistant proliferative lupus nephritis: an

Asian experience¹⁹ (Clinicaltrials.gov ID #NCT01015456). The study protocol was approved by the Ethics Committee for Human Research, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. The study was conducted under the Declaration of Helsinki of the World Medical Association, complying with International Conference on Harmonization guidelines for Good Clinical Practice.

Participants

This study utilized the data of 19 patients with proliferative LN from the EC-MPS treatment arm of the main study,¹⁹ of whom had intensive plasma MPA concentration measured. The inclusion and exclusion criteria were previously published.¹⁹ In brief, all participants had biopsy-proven LN class III/IV within 16 weeks of enrollment and proteinuria over 1.5 g/day. In addition, one should have a previous episode of active LN (relapsed) or have received initial cyclophosphamide treatment (resistant). All patients receiving EC-MPS in the main study ($n = 27$) were invited to participate in the full PK substudy. Twenty patients agreed to participate; however, one patient suffered from severe gastrointestinal side effects leading to discontinuing EC-MPS treatment. Hence, 19 patients were finally enrolled on the substudy.

All participants received 1440 mg/day (720 mg twice daily) of EC-MPS over the induction of the treatment (24 weeks). Oral prednisolone was started at 0.7 mg/kg/day and was tapered by 5 mg every 2–4 weeks, reaching 20 mg/day at week 12 and 5 mg/day at week 24. Any medications that interfere with the renin-angiotensin-aldosterone system were maintained at the same dose for 24 weeks. All participants had complete blood count, serum creatinine, urinalysis, and urine protein-creatinine ratio (UPCR) measured at baseline (week 0) and week 24. The treatment response was assessed at week 24 of the study according to the criteria previously reported in the main study.¹⁹

Concentrations of mycophenolic acid and activity of inosine-5'-monophosphate dehydrogenase enzyme

All 19 participants had plasma MPA concentrations, and a random subset of 10 participants had IMPDH activity measured at weeks 2, 8, 16, and 24 of the treatment. EDTA plasma samples were collected at predose (0), 0.5, 1, 2, 3, 4, 8, and 12 h postdose to quantify plasma MPA. In addition, lithium heparin plasma samples were collected at predose (0), 0.5, 1, 2, 3, 4, and 8 h postdose to measure IMPDH activity.

Plasma MPA concentrations were measured using a fully validated high-performance liquid chromatography (HPLC) technique (Shimadzu Corporation). Sample preparation was performed with protein precipitation using 0.1 M phosphoric acid in acetonitrile. An internal standard was phenolphthalein glucuronide. Separation was performed by a reversed-phase HPLC using a Zorbax Eclipse XDB C18 column (150 mm × 4.6 mm, 5 μm particle size; Agilent Technologies). The analytes were eluted under gradient conditions using a mobile phase consisting of methanol and 0.15% phosphoric acid. A linear calibration curve of the concentrations ranged from 0.2–50 μg/ml with $r^2 > 0.999$. Intra- and inter-day precisions were 1.04–3.68% and 1.89–3.28%, respectively. The accuracy was 93–109%. The mean absolute recovery of all three analytes was >93%.

IMPDH activity was quantified as previously reported.²⁰ In brief, the assay was based on the incubation of peripheral blood mononuclear cells' (PBMCs) lysates with inosine monophosphate (IMP) and nicotinamide adenine dinucleotide (NAD). After incubation, xanthosine monophosphate (XMP) was determined by a reversed-phase HPLC with Luna 5u C18 column (250 mm × 4.6 mm, 5 μm; Phenomenex). The analytes were then eluted under gradient conditions using methanol and buffer containing 7 mmol/L of tetra-*n*-butyl ammonium hydrogen sulfate and 50 mmol/L of potassium dihydrogen phosphate. A linear calibration curve of XMP and adenosine monophosphate (AMP) covered concentrations ranged from 2 to 200 and 1 to 200 μmol/L, respectively ($r^2 > 0.999$). Intra- and inter-day precisions of XMP were 0.39–1.49 and 0.63–2.63%, respectively. The accuracy was 94–106%. The mean absolute recovery was greater than 98%. The IMPDH activity was calculated from the number of moles of XMP produced per second per moles of AMP using the following equation: IMPDH activity (μmol/s/mol AMP) = [produced XMP (μmol/L) × 106] / [incubation time (s) × measured AMP (μmol/L)].²⁰

Pharmacokinetics, pharmacodynamics, and statistical analyses

PK analyses were performed as noncompartmental analyses with Phoenix WinNonlin version 8.3 (Cetara USA, Inc.). PK parameters of interest included C₀ (μg/ml), maximum plasma MPA concentration (C_{max} ; μg/ml), time to maximum plasma MPA concentration (T_{max} ; h), and MPA-AUC_{0–12h} (μg.h/ml). The predicted free form of C₀ (predicted freeC₀; μg/ml) were calculated as $[-9.76] + [16.56 \times \text{serum creatinine (mg/dl)}] + [7.01 \times \text{total MPA C}_0 \text{ (}\mu\text{g/ml)}]$ and predicted MPA free fraction (%) was also calculated as (predicted freeC₀/ total MPA C₀) × 100.²¹ PD parameters were

analyzed as predose IMPDH activity ($\mu\text{mol/s/mol AMP}$), minimum IMPDH activity ($\mu\text{mol/s/mol AMP}$), time to minimum IMPDH activity (h), and percentage reduction of IMPDH activity from baseline at predose (%).

Unless stated otherwise, continuous data were expressed as median (interquartile range) or mean \pm standard deviation (SD). Data were analyzed using Microsoft Excel and SPSS for Windows, version 21.0 (SPSS Inc.). Statistically significant was $p < 0.05$. The coefficient of variation (CV) in PK and PD parameters was calculated by SD/mean and presented in percentage (%CV). The Wilcoxon Signed Ranks test and Mann Whitney U test compared the dependent and independent data, respectively. Friedman test compared means of more than two groups. Correlations were analyzed using Spearman's Rho method, and stepwise linear regression was performed for $\text{MPA-AUC}_{0-12\text{h}}$. A receiver operating characteristic (ROC) curve was also constructed to assess a single timepoint of plasma MPA concentration that predicted $\text{MPA-AUC}_{0-12\text{h}} \geq 45 \mu\text{g.h/ml}$.

RESULTS

Patients' characteristics

Nineteen participants were women, aged 29 (22–43) years. All participants received 1440 mg/day of EC-MPS, and when each participant's weight was taken into account, the median dose in mg/kg/day was 23.41

(20.57–29.15) mg/kg/day. Clinical laboratory data at weeks 2, 8, 16, and 24 of the study were summarized in Table 1. When considering the changes in all clinical laboratory parameters from week 2 to week 24, no significant changes were detected except for white blood cell count (Table 1). When classifying patients according to treatment outcomes, nine participants (47%) met the response criteria¹⁹ at week 24 and were classified as responders (Table S1).

Pharmacokinetic and pharmacodynamic parameters of EC-MPS

There were no differences in plasma MPA concentrations and IMPDH activity of all participants across weeks 2, 8, 16 and 24 (Table 2, Tables S2 and S3). However, the IMPDH activity decreased from baseline by 31–42% within 2–4 h after dosing, coinciding with the increased plasma MPA concentration (Figure 1). The relationship between plasma MPA concentration and the IMPDH activity was not depicted in week 2 after EC-MPS administration but was observed from week 8 onward (Figure 1).

No statistically significant differences in all PK and PD parameters were observed across weeks 2, 8, 16, and 24 (Table 3, Tables S4 and S5). The average $\text{MPA-AUC}_{0-12\text{h}}$ reached the target of $\geq 45 \mu\text{g.h/ml}$ from week 2 (Table 3), with the percentage of patients who had

TABLE 1 Clinical characteristics of the participants at weeks 2, 8, 16, and 24

Parameters	Week 2	Week 8	Week 16	Week 24	<i>p</i> value ^a
Hemoglobin (g/dl)	10.5 (10.1–11.8)	10.6 (10.0–11.6)	11.6 (10.1–11.9)	11.0 (10.5–12.1)	0.788
White blood cell count ($\times 10^3/\mu\text{l}$)	10.3 (7.9–15.1)	9.1 (6.2–11.0)	7.7 (5.3–10.5)	7.4 (5.5–8.5) ^b	0.027
Platelet count ($\times 10^3/\mu\text{l}$)	271 (195–325)	286 (234–332)	275 (235–294)	277 (216–329)	0.819
Serum creatinine (mg/dl)	1.00 (0.78–1.23)	0.91 (0.70–1.20)	0.90 (0.70–1.10)	0.80 (0.70–1.10)	0.646
Estimated GFR (ml/min)	76.57 (65.31–106.68)	78.29 (63.52–126.04)	85.43 (69.73–109.86)	86.63 (67.11–121.06)	0.713
Albumin (g/dl)	3.20 (2.50–3.70)	3.20 (2.70–3.50)	3.20 (3.08–3.85)	3.80 (3.40–4.05) ^b	0.077
C3 (mg/dl)	77.5 (42.3–89.3)	NA	NA	80.2 (53.8–111.0)	NA
C4 (mg/dl)	16.8 (7.0–24.6)	NA	NA	20.0 (8.0–26.5)	NA
Anti-dsDNA (IU/ml)	100 (10–1039)	NA	NA	100 (10–259)	NA
Urine protein/creatinine ratio	4.00 (1.98–9.35)	3.15 (1.00–7.33)	1.70 (0.97–4.50)	1.84 (0.97–5.29) ^b	0.066
Urine RBC (cells/hpf)	5 (2–20)	3 (2–6)	3 (2–5)	2 (2–5)	0.365
Urine WBC (cells/hpf)	3 (1–10)	2 (1–3)	2 (1–5)	2 (1–3)	0.805

Note: Data are presented in the median (interquartile range).

C3, C4, and anti-dsDNA are available only on week 2 and week 24.

Abbreviations: Anti-dsDNA, anti-double stranded DNA; GFR, glomerular filtration rate; NA, not applicable; Urine RBC, urine red blood cell; Urine WBC, urine white blood cell.

^aComparison of data across weeks 2, 8, 16, and 24.

^b $p < 0.05$, comparison data of week 2 and week 24.

TABLE 2 Plasma MPA concentrations and IMPDH activity in all participants at weeks 2, 8, 16, and 24

Timepoint	Week 2	Week 8	Week 16	Week 24	<i>p</i> value ^a
Plasma MPA concentrations (<i>n</i> = 19)					
C0	2.03 (1.13–3.03)	3.69 (1.20–5.82)	2.65 (1.85–4.62)	2.89 (1.26–6.02)	0.329
C0.5	2.10 (0.96–3.48)	4.70 (1.13–6.92)	3.00 (1.61–4.46)	3.11 (1.45–5.80)	0.306
C1	2.21 (1.25–4.75)	3.94 (1.82–7.60)	2.82 (1.09–4.43)	4.17 (1.80–7.32)	0.252
C2	12.91 (4.72–27.65)	19.88 (9.51–44.38)	20.48 (5.63–36.14)	15.29 (4.52–31.07)	0.499
C3	5.57 (2.16–9.04)	9.52 (3.25–15.60)	7.07 (3.32–11.97)	7.42 (4.18–18.00)	0.171
C4	3.34 (1.33–4.68)	4.59 (1.72–6.83)	4.67 (2.21–5.70)	3.93 (2.17–6.83)	0.528
C8	2.60 (1.11–3.65)	2.46 (0.88–6.68)	3.21 (1.58–5.01)	2.21 (1.16–3.96)	0.673
C12	2.09 (1.52–3.61)	2.47 (1.77–4.24)	3.34 (1.83–4.45)	2.27 (1.35–3.42)	0.602
IMPDH activity (<i>n</i> = 10)					
C0	15.4 (12.9–21.3)	18.6 (14.1–28.8)	16.3 (12.0–32.3)	15.9 (12.0–28.0)	0.807
C0.5	16.9 (12.3–21.4)	20.4 (11.0–26.3)	18.6 (13.6–29.7)	16.4 (11.1–25.8)	0.730
C1	12.9 (12.0–17.0)	20.4 (13.7–21.9)	19.6 (13.4–26.1)	14.8 (13.2–22.5)	0.349
C2	15.1 (11.4–17.9)	14.7 (10.4–24.8)	15.5 (10.9–31.0)	14.9 (9.8–27.6)	0.923
C3	15.1 (11.5–23.8)	18.6 (12.2–24.8)	16.8 (12.2–28.9)	17.9 (10.0–25.7)	0.978
C4	16.6 (9.5–23.3)	13.9 (9.5–28.1)	16.0 (13.4–29.8)	14.5 (11.0–29.9)	0.921
C8	25.4 (8.5–34.0)	15.2 (13.9–29.3)	16.3 (8.8–26.2)	15.8 (12.1–26.8)	0.963

Note: C0, C0.5, C1, C2, C3, C4, C8, and C12: plasma MPA concentration or IMPDH activity at time 0, 0.5, 1, 2, 3, 4, 8, and 12h postdose, respectively.

Abbreviations: IMPDH, inosine-5'-monophosphate dehydrogenase; MPA, mycophenolic acid.

^aComparison of data across weeks 2, 8, 16, and 24.

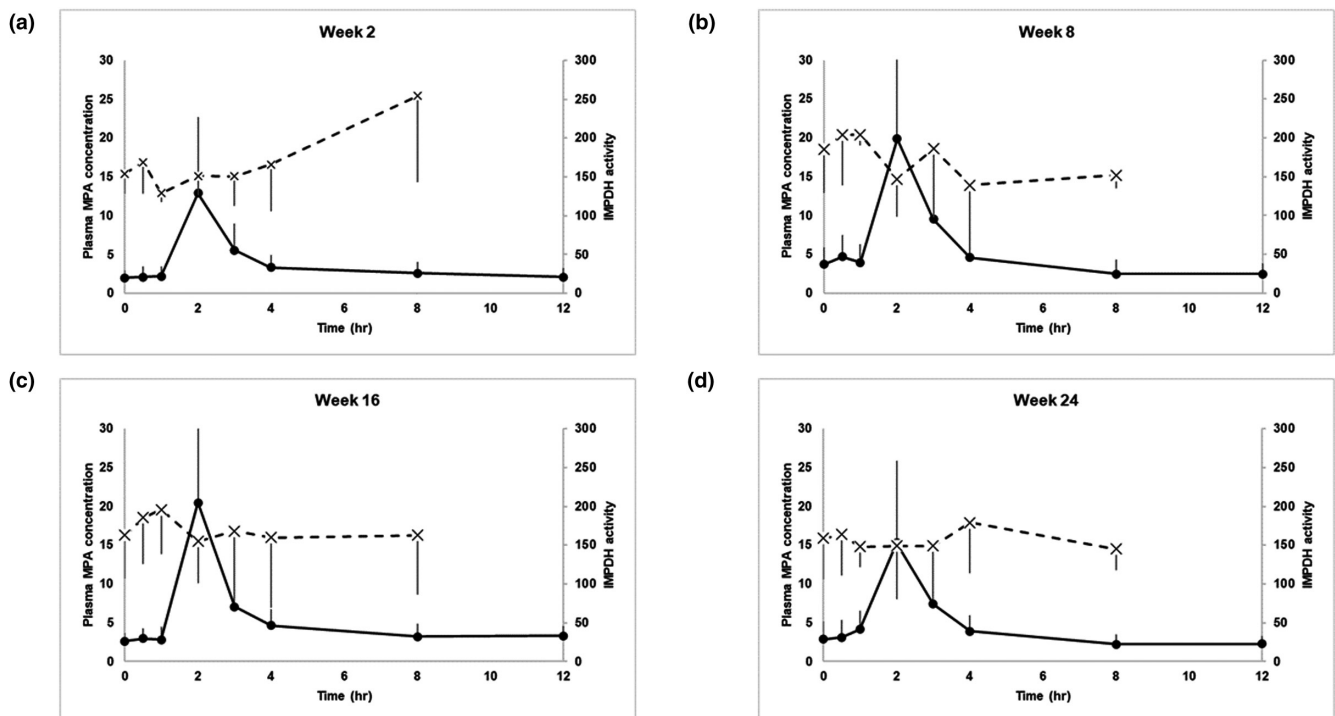


FIGURE 1 Pharmacokinetic and pharmacodynamic profiles at weeks 2 (a), 8 (b), 16 (c), and 24 (d) of enteric-coated mycophenolate mofetil in patients with lupus nephritis. Data are presented as median with median absolute deviation. IMPDH, inosine-5'-monophosphate dehydrogenase in [µmol/s/mol IMPDH]/10; MPA, mycophenolic acid in µg/ml.

TABLE 3 Pharmacokinetic and pharmacodynamic parameters of enteric-coated mycophenolate mofetil in all participants at weeks 2, 8, 16, and 24

Parameters	Week-2	%CV	Week-8	%CV	Week-16	%CV	Week-24	%CV	p value ^a
Pharmacokinetics of total form of MPA (<i>n</i> = 19)									
C ₀ (µg/ml)	2.03 (1.13–3.03)	52	3.69 (1.20–5.82)	68	2.65 (1.85–4.65)	64	2.89 (1.26–6.02)	76	0.136
C _{max} (µg/ml)	13.19 (6.39–30.09)	83	26.92 (11.04–44.38)	59	23.01 (13.78–38.94)	54	16.14 (6.21–35.54)	78	0.348
T _{max} (h)	2 (2–2)	34	2 (2–2)	24	2 (2–2.5)	20	2 (2–2)	40	0.195
MPA-AUC _{0–12h} (µg·h/ml)	47.21 (23.12–82.06)	57	77.25 (28.94–107.67)	55	68.20 (48.96–93.23)	40	53.37 (33.42–89.99)	63	0.390
Pharmacokinetics of predicted free form of MPA (<i>n</i> = 19)									
Predicted freeC ₀ (µg/ml) ^b	0.0186 (0.0141–0.0324)	56	0.0278 (0.0085–0.0470)	41	0.0209 (0.0170–0.0338)	56	0.0210 (0.0155–0.0503)	42	0.561
Predicted MPA free fraction (%) ^c	0.98 (0.86–1.35)	68	0.80 (0.74–1.37)	61	0.87 (0.77–1.16)	45	0.82 (0.74–1.13)	94	0.937
Pharmacodynamics (<i>n</i> = 10)									
Predose IMPDH activity ([µmol/s/ mol IMPDH]/10)	13.4 (12.1–18.3)	65	18.5 (13.6–44.4)	41	17.0 (12.9–23.9)	52	24.1 (14.8–35.1)	45	0.970
Time to minimum IMPDH activity after dosing (h)	4 (3–5)	50	4 (1.8–7)	87	3.5 (0.5–4)	71	2 (0.3–6.8)	79	0.423
Minimum IMPDH activity after dosing ([µmol/s/mol AMP]/10)	8.7 (7.5–12.0)	56	14.0 (8.2–24.5)	41	9.3 (7.6–13.5)	56	17.4 (12.8–21.3)	42	0.981
Percentage reduction of IMPDH activity from baseline at predose (%)	32 (13–45)	52	42 (15–50)	38	37 (26–61)	28	31 (29–31)	85	0.094

Note: Data are presented in the median (interquartile range).

Abbreviations: CV, coefficient of variation; C₀, plasma MPA concentration at time 0; C_{max}, maximum plasma MPA concentration; IMPDH, inosine-5'-monophosphate dehydrogenase; MPA, mycophenolic acid; MPA-AUC_{0–12h}, area under the plasma concentration-time of mycophenolic acid from 0 to 12h; T_{max}, time to maximum plasma MPA concentration.

^aComparison of data across weeks 2, 8, 16, and 24.

^bPredicted freeC₀ was calculated as: $-9.76 + [16.56 \times \text{serum creatinine (mg/dl)}] + [7.01 \times \text{total MPA C}_0 \text{ (}\mu\text{g/ml)}]$.²¹

^cPredicted MPA free fraction was calculated as: $[\text{Predicted freeC}_0 / \text{total MPA C}_0] \times 100$.²¹

MPA-AUC_{0-12h} \geq 45 $\mu\text{g}\cdot\text{h}/\text{ml}$ of 56, 73, 82, and 56% for weeks 2, 8, 16, and 24, respectively (Table 3).

High variability (%CV) in PK and PD parameters was observed throughout the study (Table 3). Most PK parameters in responders showed lower %CV than nonresponders, but this was not the case for PD parameters (Tables S4 and S5).

Multivariate analyses for the prediction of MPA-AUC_{0-12h}

Univariate analysis showed that MPA-AUC_{0-12h} was significantly correlated with characteristics of the patients, including EC-MPS dose/kg/day ($r^2 = 0.15$, $p = 0.002$), albumin ($r^2 = 0.28$, $p = 0.002$), UPCR ($r^2 = 0.09$, $p = 0.019$), and urine red blood cell (RBC; $r^2 = 0.10$, $p = 0.013$).

MPA-AUC_{0-12h} was moderately correlated with each single plasma MPA concentration timepoint: C0 ($r^2 = 0.45$, $p = 0.000$), C0.5 ($r^2 = 0.39$, $p = 0.000$), C1 ($r^2 = 0.12$, $p = 0.005$), C2 ($r^2 = 0.51$, $p = 0.000$), C3 ($r^2 = 0.41$, $p = 0.000$), C4 ($r^2 = 0.44$, $p = 0.000$), C8 ($r^2 = 0.56$, $p = 0.000$), C12 ($r^2 = 0.38$, $p = 0.000$), and predicted freeC0 ($r^2 = 0.41$, $p = 0.000$). Additionally, MPA-AUC_{0-12h} was also associated with IMPDH activity at C3 and C4 ($r^2 = 0.14$, $p = 0.001$ and $r^2 = 0.28$, $p = 0.000$, respectively).

Multivariate analyses confirmed that independent of dose, albumin, UPCR, and urine RBC, each of the single plasma MPA concentrations at C0 to C12, except C1 and the predicted freeC0, were independent predictors of MPA-AUC_{0-12h} (Table 4). From all significant associations, C0.5, C2, C3, C4, and C8 had the model's adjusted $r^2 > 0.5$ (Table 4). Unlike plasma concentrations, only the

TABLE 4 Predictors of MPA-AUC_{0-12h} for enteric-coated mycophenolate mofetil in lupus nephritis

Time point	^a Model adjusted r^2	Significant predictors in the model	Regression coefficient	95% confidence interval	p value
C0	0.484	C0	4.902	(0.569, 9.335)	0.028
		Dose/kg/day	2.509	(0.857, 4.161)	0.004
		Urine RBC	-1.023	(-1.797, -0.249)	0.011
C0.5	0.516	C0.5	4.106	(0.908, 7.305)	0.013
		Dose/kg/day	2.781	(1.277, 4.284)	0.001
		Urine RBC	-1.046	(-1.046, -0.316)	0.006
C1	0.268	Albumin	29.379	(13.325, 45.432)	0.001
C2	0.514	C2	1.098	(0.775, 1.873)	0.000
		Albumin	21.782	(8.348, 35.217)	0.002
C3	0.540	C3	1.451	(0.533, 2.369)	0.003
		Dose/kg/day	2.782	(1.389, 4.176)	0.000
		Urine RBC	-1.043	(-1.738, -0.348)	0.004
C4	0.611	C4	3.897	(2.042, 5.752)	0.000
		Dose/kg/day	2.513	(1.213, 3.812)	0.000
		Urine RBC	-0.963	(-1.603, -0.323)	0.004
C8	0.719	C8	6.897	(5.005, 8.789)	0.000
		Albumin	25.397	(15.411, 35.283)	0.000
C12	0.489	C12	8.880	(4.422, 13.338)	0.000
		Albumin	17.040	(2.387, 31.694)	0.024
Predicted freeC0	0.244	Albumin	27.736	(10.921, 44.551)	0.002
IMPDH at C3	0.187	Dose/kg/day	2.953	(0.344, 5.561)	0.029
IMPDH at C4	0.325	Albumin	29.881	(6.749, 53.012)	0.002
		IMPDH at C4	0.142	(0.013, 0.271)	0.033

Note: C0, C0.5, C1, C2, C3, C4, C8, and C12, plasma MPA concentration at times 0, 0.5, 1, 2, 3, 4, 8, and 12h postdose, respectively.

Dependent variable: MPA-AUC_{0-12h}.

Abbreviations: IMPDH, inosine-5'-monophosphate dehydrogenase; MPA-AUC_{0-12h}, area under the plasma concentration-time profile of mycophenolic acid from 0-12h; UPCR: urine protein creatinine ratio; urine RBC: urine red blood cell count.

^aAdjusted for dose/kg/day, albumin, UPCR, and urine RBC.

The bold figures represent the single plasma timepoint models that had the model adjusted $r^2 > 0.5$.

IMPDH activity at C4 showed a weak association with $\text{MPA-AUC}_{0-12\text{h}}$ in the multivariate analyses (Table 4).

ROC curves

For clinical implementation, ROC curves were constructed for C0.5, C2, C3, C4, and C8 to find the optimal cutoff value of plasma MPA concentration at each timepoint corresponding with $\text{MPA-AUC}_{0-12\text{h}} \geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ (Figure 2a–f).

Plasma MPA concentration at C0.5 had the largest ROC area (0.951; Figure 2). The acceptable specificity of the cutoff value was set at 88.2%, and the proposed cutoff value of plasma MPA concentration at each timepoint are shown in Table 5. With 88.2% specificity, plasma MPA concentrations at C0.5 and C8 showed the highest sensitivity (85%) with the cutoff value of ≥ 2.03 and $\geq 1.81 \mu\text{g}/\text{ml}$, respectively. Plasma MPA concentrations at C2 and C3 also showed favorable sensitivity (82.5% with the cutoff value of ≥ 12.70 and $\geq 6.20 \mu\text{g}/\text{ml}$, respectively). Of note, responders showed a better percentage of participants reaching target cutoff values in all proposed timepoints (Table 5), supporting the ability of these cutoffs in clinical practice.

Combining data from the multivariate analysis (Table 4) and ROC curves (Table 5, Figure 2), together with the practicality to be used in the clinical setting,

$\text{C0.5} \geq 2.03 \mu\text{g}/\text{ml}$ seemed to be the best choice for TDM in patients with LN treated with EC-MPS.

DISCUSSION

This study has demonstrated a potential benefit of TDM for EC-MPS treatment of patients with relapsed or resistant LN. In the original study,¹⁹ EC-MPS has shown comparable efficacy to intravenous cyclophosphamide. In this substudy, the PKs and PDs of EC-MPS may explain its efficacy by adequate MPA exposure. Changes in the plasma MPA concentration-time profiles were related to the PD profiles represented by the IMPDH activity. Furthermore, plasma MPA concentration at specific timepoints (C0.5, C2, C3, C4, and C8) were predictors of $\text{MPA-AUC}_{0-12\text{h}}$. In particular, plasma MPA concentration at $\text{C0.5} \geq 2.03 \mu\text{g}/\text{ml}$ was an excellent surrogate marker for predicting $\text{MPA-AUC}_{0-12\text{h}} \geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$.

In this difficult-to-treat LN, we found the interrelationships between the PKs and PDs of MPA for the first time for EC-MPS. The relationships were evidenced from week 8 onward (Figure 1). Changes in PKs and PDs were previously reported in childhood-onset SLE treated with MMF.¹⁴ At steady-state, the IMPDH activity decreased with increasing plasma MPA concentrations during 9 h postdose, with the maximum inhibition of IMPDH coinciding with $\text{MPA-C}_{\text{max}}$. Similar findings were also

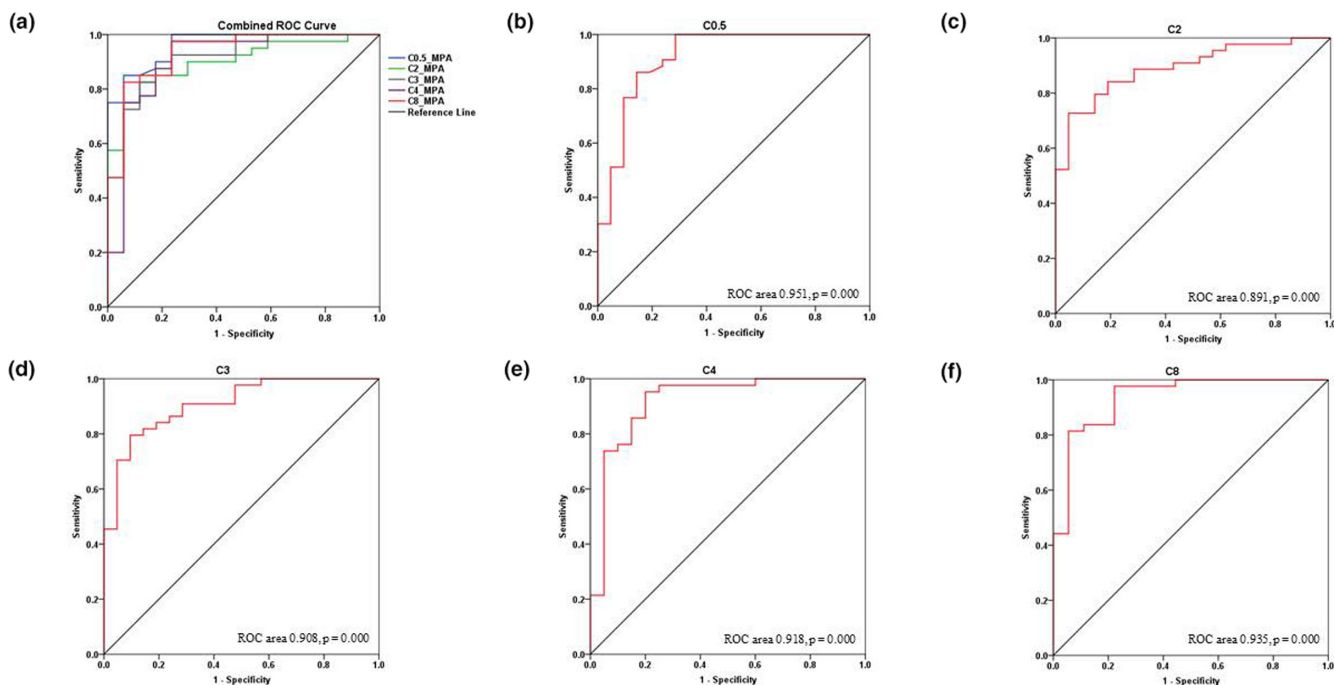


FIGURE 2 Receiver operating characteristic curves for a prediction of $\text{MPA-AUC}_{0-12\text{h}} \geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ by single plasma MPA concentration in the treatment with enteric-coated mycophenolate mofetil in lupus nephritis. C0.5, C2, C3, C4, and C8, plasma MPA concentration at times 0.5, 2, 3, 4, and 8 h postdose, respectively; MPA, mycophenolic acid; $\text{MPA-AUC}_{0-12\text{h}}$, area under the plasma concentration-time profile of mycophenolic acid from 0–12 h; ROC, receiver operating characteristic.

TABLE 5 Proposed single time point plasma MPA concentration cutoff value to predict $\text{MPA-AUC}_{0-12\text{h}} \geq 45 \mu\text{g}\cdot\text{h}/\text{ml}$ for the treatment with enteric-coated mycophenolate mofetil in lupus nephritis

Time point	Proposed plasma MPA concentration cutoff value ($\mu\text{g}/\text{ml}$)	Sensitivity (%) with specificity of 88.2%	Participants (%) reach target cutoff value		
			All ($n = 19$)	Responders ($n = 9$)	Nonresponders ($n = 10$)
C0.5	≥ 2.03	85.0	62	77	50
C2	≥ 12.70	82.5	57	61	53
C3	≥ 6.20	82.5	67	87	50
C4	≥ 3.79	77.5	53	60	47
C8	≥ 1.81	85.0	61	61	61

Note: C0.5, C2, C3, C4, and C8, plasma MPA concentration at times 0.5, 2, 3, 4, and 8 h postdose, respectively.

Abbreviations: MPA, mycophenolic acid; $\text{MPA-AUC}_{0-12\text{h}}$, area under the plasma concentration-time profile of mycophenolic acid from 0–12 h.

described in adult kidney transplant recipients who received MMF.¹⁵ In our study, the magnitude of maximum IMPDH reduction from predose was 30–40%, which is comparable to those in children (29%),¹⁴ but not kidney transplantation (47%).¹⁵

In the original study,¹⁹ EC-MPS has a comparable efficacy but a higher safety profile than the comparator treatment. Therefore, it was recommended that EC-MPS should be a favorable choice of treatment in difficult-to-treat LN.¹⁹ Adequate MPA dose is a significant factor in reaching the plasma therapeutic target. Many Thai patients with LN received subtherapeutic doses of EC-MPS ranging from 1080 to 1440 mg/day.⁵ In a study comparing a fixed-dose or a concentration-controlled, EC-MPS dose was adjusted according to the clinical response or plasma MPA concentrations, and plasma MPA was crucial for achieving therapeutic response.¹³ However, plasma MPA concentrations of both previous studies^{5,13} tended to be low and were not steady for the whole study period; whereas in our study, average plasma MPA concentrations reached sustainable therapeutic levels until the 24-week time without any dose adjustment. Additionally, C_0 , C_{max} , and MPA-AUC of EC-MPS in our study were higher than those in the previous reports,^{5,13} confirming the use of 1440 mg/day as the optimum therapeutic dose of EC-MPS.

Free (or unbound) drug concentrations are responsible for the pharmacological response of drugs.²¹ Here, the predicted plasma free C_0 and the predicted MPA free fraction were calculated.²¹ The predicted plasma free C_0 (Table 3) was similar to a study in patients with LN receiving 2000 mg/day of MMF (0.02164 $\mu\text{g}/\text{ml}$)¹¹ but was higher than that of the study in patients with LN treated with EC-MPS (0.0101 and 0.0119 $\mu\text{g}/\text{ml}$ for fixed dose and concentration-controlled arms, respectively).¹³ These differences may be, in part, due to the differences in EC-MPS dose described above. Moreover, the predicted MPA free fraction in our study (Table 3) was consistent with

previous reports in patients with LN receiving either MMF (1.05%)¹¹ or EC-MPS (0.90%).¹³

We observed high variability in PK parameters of EC-MPS (Table 3, Tables S4 and S5). These data were consistent with a previous report in renal transplantation²² where high inter- and intrasubject variability of MMF and EC-MPS was noted, and this study suggested that MPA trough concentrations had limited value in terms of TDM for either MMF or EC-MPS. Our results were also similar to a previous study in the Thai population,⁵ MMF and EC-MPS showed high %CV in MPA-AUCs, C_{max} , and T_{max} (50%, 62%, and 67%, respectively for MMF; and 23%, 50%, and 77%, respectively for EC-MPS). However, our %CV for T_{max} was relatively low (34%, 24%, 20%, and 40% for weeks 2, 8, 16, and 24, respectively; Table 3). On the other hand, our %CV for MPA-AUCs was relatively high (57%, 55%, 40%, and 63% for weeks 2, 8, 16, and 24, respectively; Table 3) compared to the previous report.⁵ Reported factors affecting PKs and PDs of MPA include renal function, serum albumin and urinary protein excretion, gender, ethnicity, food, comedication, disease severity and genetics of drug-metabolizing enzymes, drug transporters, and drug target genes.^{23–26} Our cohort was homogenous in all factors mentioned above, except there were no data regarding polymorphisms in genes encoded for MPA disposition or the mechanism of action (i.e., the uridine diphosphate-glucuronosyltransferase [UGT], the human organic anion transporting polypeptide family [OATP], multidrug-resistant protein-2 [MRP-2], IMPDH1, and IMPDH2). A population pharmacogenetic-PK study of EC-MPS in Korean kidney transplant recipients identified renal function together with *SLCO1B1* and *UGT1A9* genotypes as significant covariates affecting the pharmacokinetics of EC-MPS.²⁶ A recent systematic review and meta-analysis suggested six single-nucleotide polymorphisms (SNPs) that were significantly associated with PK variability or adverse

effects of MPA.²⁷ A genetic-guided study is warranted to confirm these SNP roles in LN.

Several studies in patients with severe LN treated with MMF found various single timepoints of plasma MPA concentrations significantly associated with targeted MPA-AUC.^{5,7,9-12} These timepoints included C0,^{5,7,9-11} C1,^{5,9,12} C1.5,⁷ C2,^{7,12} C3,^{7,9} C6,^{7,9} and C12.¹² Based on our previous study in severe LN receiving either MMF or EC-MPS,⁵ favorable treatment response rates were associated with MPA-AUC₀₋₁₂ ≥ 45 μg.h/ml regardless of MPA formulation, and this target MPA-AUC was implemented clinically.⁶ In that study, only the MMF patients showed a high association between plasma MPA C1 and MPA-AUC ($r = 0.92, p < 0.001$). No such associations were observed in the EC-MPS treated patients. The authors also proposed that plasma MPA-C1 ≥ 13 μg/ml independently predicts MPA-AUC₀₋₁₂ ≥ 45 μg.h/ml.⁵ Unlike MMF, it remains unclear whether a single timepoint of plasma MPA concentration would be associated with MPA-AUC₀₋₁₂ ≥ 45 μg.h/ml in those taking EC-MPS.^{5,18} Interestingly, Ranganathan et al. reported that plasma total and free MPA concentrations at C0, C2, and C12 moderately correlated with MPA-AUC_{0-12h} in patients with severe LN receiving EC-MPS.¹³

In this study, each plasma MPA concentration at C0.5, C2, C3, C4, and C8 were significantly associated with targeting MPA-AUC_{0-12h} ≥ 45 μg.h/ml with the cutoff point of plasma MPA level 2.03, 12.70, 6.20, 3.79, and ≥ 1.81 μg/ml, respectively. In addition, these timepoints also show high sensitivity and specificity from the ROC curve (Table 5). Therefore, for practical use, together with the highest sensitivity (85%; Table 5), we proposed that plasma MPA-C0.5 would be the single timepoint of choice for TDM of EC-MPS (MPA-AUC_{0-12h} ≥ 45 μg.h/ml) with a cutoff point of ≥ 2.03 μg/ml. However, a prospective TDM-guided study in larger cohort sizes, including male and female patients, is still required to confirm the role of plasma MPA-C0.5 ≥ 2.03 μg/ml in predicting target MPA-AUC and evaluating the relationship of the cutoff point to treatment outcomes.

There are other limitations to the study. This study was a retrospective analysis even though samples were collected during a prospective study. As a substudy, this study's sample size lacked the power to evaluate associations between PKs and PDs of EC-MPS to treatment outcomes. However, we noted that responders tended to have less PK parameters variability than nonresponders (Tables S4 and S5). In addition, the free form of plasma MPA concentrations was not measured, but because the %predicted MPA free fraction was relatively small (Table 3), the use of the total form seemed sufficient to conduct TDM. This study cannot determine the link between single plasma concentration TDM with concerned MPA side effects, such as bone marrow depression or

gastrointestinal side effects, as the study lacked the power to do so. However, one patient who agreed to participate in this substudy suffered from gastrointestinal side effects and had to stop EC-MPS. Thus, this patient was not enrolled on the substudy. There was a large gap between the sampling time of C8 and C12; therefore, the enterohepatic recirculation of MPA in the concentration-time profile cannot be thoroughly evaluated. Regarding the IMPDH activity measurement, the assays were conducted ex vivo in washed PBMCs and, therefore, might not fully represent the in vivo activity.

Further studies with more detailed sampling time investigating the roles of MPA metabolites in plasma, genetic variations of drug-metabolizing enzymes, drug transporters, or drug targets involved in the pathway of EC-MPS metabolism and mechanisms, together with the measurement of IMPDH activity in a larger cohort size would give insight into the whole picture of PK and PD changes in patients with LN using EC-MPS.

In conclusion, patients with relapsed or resistant LN treated with EC-MPS had predictable PKs of MPA coinciding with a reduction of IMPDH activity, a PD marker. Therefore, TDM of EC-MPS may be conducted using a single timepoint of plasma MPA-C0.5 with the proposed cutoff at ≥ 2.03 μg/ml.

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CONFLICT OF INTEREST

All authors declare no competing interests for this work.

AUTHOR CONTRIBUTIONS

P.C., W.P., W.K., and Y.A. wrote the manuscript. P.C., W.P., S.A., and Y.A. designed the research. W.P., C.R., S.A., P.C., and Y.A. performed the research. P.C., W.P., W.K., and Y.A. analyzed the data.

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SUPPORTING INFORMATION

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