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Pharmacokinetics of Enteric-Coated Mycophenolate Sodium in Lupus Nephritis (POEMSLUN)

Dwarakanathan Ranganathan, MD, DM, FRCP, FRACP,† Mohd H. Abdul-Aziz, PhD,‡ George T. John, MD, DM, FRCP, FRACP,* Brett C. McWhinney, MPhil,§ Robert G. Fassett, PhD,‡ Helen Healy, PhD,*‡ Paul Kubler, FRACP,¶ Aaron Lim, MBBS,* Jeffrey Lipman, PhD,‖ Megan Purvey, MBBS,* Matthew Roberts, PhD,* Reza Reyaldeen, FRACP,* Jacobus Ungerer, PhD,§ and Jason A. Roberts, PhD‡‖**††*

Background: Mycophenolate mofetil or enteric-coated mycophenolate sodium (EC-MPS) and steroids are used for induction and maintenance therapy in severe lupus nephritis. Blood concentrations of mycophenolic acid (MPA), the active metabolite of these drugs, vary among patients with lupus nephritis. The objective of this study was to examine whether concentration-controlled (CC) dosing (through therapeutic drug monitoring) of EC-MPS results in a higher proportion of participants achieving target exposure of MPA compared with fixed-dosing (FD). An additional aim of the study was to evaluate the influence of CC dosing on clinical outcomes.

Methods: Nineteen participants were randomly assigned either to the FD or CC group. All the participants were eligible to have free and total measurements of MPA over a period of 8–12 hours on 3 different occasions. Area under the concentration–time curve between 0 and 12 hours ($AUC_{0\text{-}12}$) was calculated using noncompartmental methods. Dose of EC-MPS was titrated according to $AUC_{0\text{-}12}$ in the CC group.

Results: Thirty-two $AUC_{0\text{-}12}$ measurements were obtained from 9 FD and 9 CC participants. Large inter-patient variability was observed in both groups but was more pronounced in the FD group. There were no significant differences between FD and CC participants in any pharmacokinetic parameters across the study visits, except for total C_0 (FD 2.0 ± 0.3 mg/L versus CC 1.1 ± 0.3; P = 0.01) and dose-normalized C_0 (FD 2.9 ± 0.2 mg/L/g versus CC 2.1 ± 0.7 mg/L/g; P = 0.04) at the second visit and total $AUC_{0\text{-}12}$ (FD 66.6 ± 6.0 mg·h/L versus CC 35.2 ± 11.4 mg·h/L; P = 0.03) at the third visit. At the first study visit, 33.3% of the FD and 11.1% of the CC participants achieved the target area under the concentration–time curve (P = 0.58). From the second visit, none of the FD participants, compared with all the CC participants, achieved target $AUC_{0\text{-}12}$ (P = 0.01). More CC participants achieved remission compared with FD participants (absolute difference of −22.2, 95% confidence interval −0.19 to 0.55; P = 0.62). The mean free MPA $AUC_{0\text{-}12}$ was significantly lower in those who had complete remission.

Conclusions: CC participants reached target $AUC_{0\text{-}12}$ quicker. Larger studies are required to test clinical efficacy.

Key Words: pharmacokinetics, TDM, EC-MPS, LN

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INTRODUCTION

Regional and international guidelines are available for the management of lupus nephritis (LN) for both adult and pediatric populations.[1–5] These guidelines advocate steroids

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From the *Department of Renal Medicine, Royal Brisbane and Women's Hospital; †School of Medicine, Griffith University; ‡Faculty of Medicine, University of Queensland Centre for Clinical Research (UQCCR), The University of Queensland; §Pathology Queensland, Royal Brisbane and Women's Hospital; Departments of ¶Rheumatology; and ‖Intensive Care Medicine, Royal Brisbane and Women's Hospital; **Pharmacy Department, Royal Brisbane and Women's Hospital; and ††Centre for Translational Anti–Infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Queensland, Australia.

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D. Ranganathan, G. T. John, and J. A. Roberts designed the study and wrote the protocol. H. Healy and R. G. Fassett advised and reviewed the study protocol. P. Kubler was involved with study recruitment. B. C. McWhinney, J. A. Roberts, and J. Ungerer were involved in the analysis of samples. A. Lim, M. J. Roberts, M. Purvey, and R. Reyaldeen were involved in the collection of blood samples. M. H. Abdul-Aziz assisted in the data analysis and preparation of the manuscript. All authors read and approved the final version of the manuscript.

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The study was conducted in accordance with Good Clinical Practice Guidelines, the principles that have their origins in the "Declaration of Helsinki" adopted by the World Medical Association in October 1996, the National Health and Medical Research Council (NHMRCC) National Statement on Ethical Conduct in Human Research (2007), or replacement or other relevant NHMRC publication or guideline that relates to clinical trials.

Correspondence: Dwarakanathan Ranganathan, MD, FRCP, FRACP, Department of Renal Medicine, Royal Brisbane and Women's Hospital, Butterfield St, Herston 4029, Australia (e-mail: Dwarakanathan.ranganathan@health.qld.gov.au).

and mycophenolic acid (MPA) prodrugs, mycophenolate mofetil (MMF), or enteric-coated mycophenolate sodium (EC-MPS) for induction and maintenance therapy in class III, IV, and V LN.[3] Guidelines recommend gradual dose titration of MMF to 2000–3000 mg/d as induction therapy and 1000–2000 mg/d as maintenance treatment to achieve the best possible toxicity/efficacy ratio.[3] An equivalent dose of EC-MPS at 1440–2160 mg is administered as induction therapy.[6] The dose of MMF varies in clinical studies, and this partly accounts for variable efficacy. Furthermore, adverse events lead to dose reduction and suboptimal outcome.[7] Therapeutic drug monitoring (TDM) is used to maximize the efficacy and minimize the side effects with therapy based on exposure rather than dose.[8] It is unclear whether the TDM of MPA, the active entity, and dose modulation of its prodrugs (MMF/EC-MPS) would improve outcomes in LN patients. Although some studies have shown that the area under the concentration–time curve (AUC) of 35–45 mg·h/L of MPA is associated with remission and therapeutic efficacy, there are no randomized controlled trials.[9–13] Administration of 1000 mg of MMF and equivalent 720 mg of EC-MPS results in a similar 12-hour MPA AUC,[6] although the pharmacokinetic profiles of MMF and EC-MPS differ. There are limited data on concentration-controlled (CC) EC-MPS dosing (through TDM) in LN patients. In addition, there are no data on free MPA pharmacokinetics and relationship to outcome in LN patients treated with EC-MPS. This is important in LN patients with hypoalbuminemia because MPA is highly protein-bound and the unbound drug is responsible for the pharmacological effect. We therefore performed a randomized controlled trial to determine whether CC dosing of EC-MPS through TDM results in a higher proportion of participants achieving target MPA exposure range in LN compared with fixed-dosing (FD). We also report on the efficacy of EC-MPS in both groups and free MPA exposure on their clinical outcome.

MATERIALS AND METHOD

The protocol of POEMSLUN has previously been published.[14]

Ethical Considerations

The Human Research Ethics Committee of the Royal Brisbane and Women's Hospital (HREC/10/QRBW/426) approved this study. The study was registered on the Australia New Zealand Clinical Trial Registry ACTRN12611000798965.

Participants

The participants who fulfill the inclusion and exclusion criteria were recruited from in-patients at Royal Brisbane and Women's Hospital Renal and Rheumatology Departments or patients attending the Renal Rheumatology Lupus Vasculitis Clinic. All participants who had biopsy-proven class III/IV/V LN and aged 18 years or older and received EC-MPS for more than 2 weeks either as induction or maintenance therapy were eligible for recruitment. All consenting participants were randomized to the CC or FD group. The participants were stratified to the induction and maintenance phase of treatment with EC-MPS.

Randomization

Participants were block randomized into group 1 or 2 in permuted block sizes of 2 and 4 with 33 and 66% respectively; stratified for induction and maintenance therapy. Owing to the nature of intervention, research staff members, except the laboratory bioanalysts and participants, were not masked to the treatment allocation. The participants were followed up for 12 months after the last participant was recruited.

Study Intervention

Group 1: Fixed-Dosing

Oral EC-MPS 30 mg/kg body weight was administered to induce remission. EC-MPS dosage was reduced by 180 mg

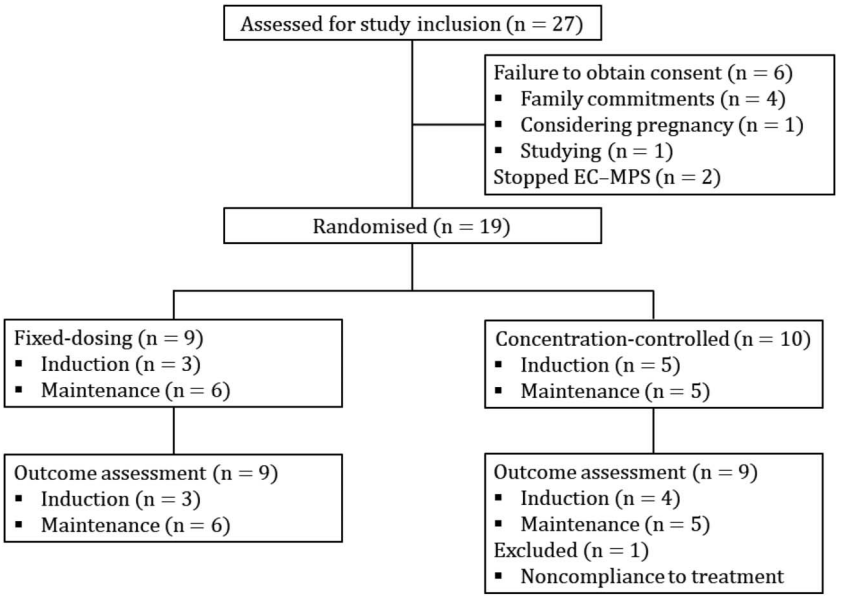

FIGURE 1. Study flow chart.

TABLE 1. Baseline Demography and Clinical Characteristics of the Study Population*

	Fixed-Dosing (n = 9)	Concentration-Controlled (n = 9)	*P*†
Age (in yr)	47.6 ± 16.0	50.9 ± 14.0	0.64
Sex, n (%)			
Male	2 (22.2)	2 (22.2)	1.00
Female	7 (77.8)	7 (77.8)	
Race, n (%)			
White	8 (88.9)	7 (77.8)	0.38
Asian	0 (0.0)	1 (11.1)	
Hispanic	0 (0.0)	1 (11.1)	
Others	1 (11.1)	0 (0.0)	
Weight (kg)	75.5 ± 14.2	81.0 ± 24.2	0.57
Renal pathology, n (%)			
ISN/RPS class III	2 (22.2)	2 (22.2)	1.00
ISN/RPS class IV	5 (55.6)	5 (55.6)	
ISN/RPS class V	2 (22.2)	2 (22.2)	
Serum creatinine (μmol/L)	99.9 ± 40.7	83.9 ± 42.8	0.43
eGFR (mL/min/1.73 m^2)	67.3 ± 25.0	88.1 ± 39	0.20
eGFR classification, n (%)			
Urine protein (g/24 hours)	1.4 ± 1.5	2.9 ± 3.8	0.39
Urine protein/creatinine ratio	38.0 (10.5–174.0)	18.0 (6.5–557.5)	0.80
Serum albumin (g/L)	36.4 ± 5.6	34.0 ± 8.9	0.50
Serum complement (g/L)			
C3	0.8 ± 0.3	1.0 ± 0.4	0.36
C4	0.2 ± 0.1	0.2 ± 0.1	0.94
AntidsDNA	33.0 ± 24.8	48.1 ± 38.6	0.46
EC-MPS dose (g/d)	1.44 (0.45–1.44)	1.44 (0.54–1.44)	0.78
EC-MPS dose (g/kg/d)	0.01 (0.01–0.02)	0.02 (0.01–0.03)	0.67
Prednisolone dose (mg/d)	10.0 (5.0–15.0)	8.0 (5.0–40.0)	0.86

*Data are presented as mean ± SD or median (interquartile range) for continuous variables and number and percentage for categorical variables.

†Continuous variables were compared using the *t*-test or Mann–Whitney *U*-test as appropriate, and dichotomous variables were compared using the Pearson χ^2 test or Fisher exact test as appropriate.

ALP, alkaline phosphatase; ALT, alanine transaminase; Anti-dsDNA, anti–double-stranded DNA; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; BMI, body mass index; EC-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; ISN/RPS, International Society of Nephrology/Renal Pathology Society.

twice daily on achieving complete remission or if there were side effects or if the total white cell count was $<3500/mm^3$.

Group 2: Concentration-Controlled

The oral EC-MPS dose was titrated according to the $AUC_{0\text{-}12}$, tested at the first visit, and adjusted to a target $AUC_{0\text{-}12}$ of 40–60 mg·h/L at the second visit. The dosage was reduced if the $AUC_{0\text{-}12}$ was above 60 mg·h/L. Once there was a remission or if participants were randomized at the maintenance phase of treatment, the $AUC_{0\text{-}12}$ of 30–50 mg·h/L was maintained. Both groups received similar management other than EC-MPS dosing.

Data Collection

At the time of entry to the study, clinical and demographic data were collected for each participant, including age, sex, weight, height, allergies, clinical information, other comorbidities, and concomitantly prescribed drugs. Laboratory investigations were performed every 12 weeks consisting of a urine sediment examination, 24-hour urinary protein measurement, and/or urine protein to creatinine ratio (uPCR), renal function assessments-eGFR, liver function tests, complement components C3 and C4, antinuclear antibody, anti–double-stranded DNA antibody, and pharmacokinetic analysis of MPA.

Pharmacokinetic Sampling

Pharmacokinetic analysis of MPA was performed at different time points. Participants who entered the study at the induction phase had their first analysis at 1–2 months, the second at 3–4 months, and the third at 7–9 months. The protocol was amended, and the participants in the maintenance phase had their assays at the time of entry and the second at 3 months later. Where participants were unable to attend for a 12-hour AUC determination, we extrapolated $AUC_{0\text{-}12}$ from an 8-hour AUC determination as has been used elsewhere.[14] Blood samples were collected before and after the EC-MPS dose at 15-time points for the 8-hour group and, where participant consented, 17 samples for the 12-hour group. The pharmacokinetic values were calculated using noncompartmental methods. The $AUC_{0\text{-}12}$ was calculated using the trapezoidal rule.

Bioanalysis

Total plasma MPA concentrations were determined using a validated ultra-high performance liquid chromatography–tandem mass spectrometry method. MPA-d3 internal standard (Toronto Research Chemicals, Toronto, ON, Canada) in methanol was added to plasma, vortexed, and centrifuged before analysis by UHPLC using an Acquity UPLC HSS T3 C18 analytical column (1.8 μm, 2.1 × 100 mm) and Acquity BEH C18 precolumn (1.7 μm, VanGuard 2.1 5 mm) (Water Corporation, Milford, MA) maintained at 40°C, with gradient elution using 2-mM ammonium acetate and 0.1% formic acid in water (mobile phase A) and 2-mM ammonium acetate and 0.1% formic acid in methanol (mobile phase B). Multiple reaction monitoring was conducted using positive electrospray ionization and detection of MPA (321.2 > 207.2) and MPA-d3 (324.3 > 310.2 transitions (Water Corporation).

Ultrafiltrates of plasma-free mycophenolate were prepared by equilibrating 500 μL of plasma at 37°C for 30 minutes

TABLE 2. Summary of Pharmacokinetic Sampling and Pharmacokinetic Parameters of Total and Free Mycophenolic Acid in the Study Population*

Total No. of MPA AUCs	32
No. of MPA AUCs per study visit, n (%)	
First visit†	18 (56.3)
Second visit‡	9 (28.1)
Third visit§	5 (15.6)

	First Visit			Second Visit			Third Visit		
	FD, n = 9	CC, n = 9	P¶	FD, n = 4	CC, n = 5	P¶	FD, n = 2	CC, n = 3	P¶
Total MPA concentration									
$AUC_{0\text{-}12}$ (mg·h/L)	49.0 ± 35.5	29.0 ± 16.6	0.15	62.4 ± 39.4	35.0 ± 3.9	0.26	66.6 ± 6.0	35.2 ± 11.4	**0.03**
Dose-normalized $AUC_{0\text{-}12}$ (mg·h/L/g)	117.9 ± 94.1	45.5 ± 27.1	0.05	92.9 ± 54.3	62.1 ± 6.3	0.34	92.5 ± 8.2	75.2 ± 17.4	0.37
C_0 (mg/L)	1.8 ± 1.3	1.2 ± 0.2	0.30	2.0 ± 0.3	1.1 ± 0.3	**0.01**	2.0 ± 0.0	2.7 ± 0.5	0.31
Dose normalised C_0 (mg/L/g)	4.6 ± 3.9	2.2 ± 1.5	0.14	2.9 ± 0.2	2.1 ± 0.7	**0.04**	2.8 ± 0.0	5.1 ± 1.2	0.23
C_{max} (mg/L)	15.5 ± 6.6	11.1 ± 7.1	0.20	23.4 ± 15.1	16.5 ± 6.3	0.44	17.0 ± 4.1	14.5 ± 15.1	0.86
Dose-normalized C_{max} (mg/L/g)	43.5 ± 39.8	15.3 ± 8.4	0.08	35.4 ± 21.9	29.2 ± 11.5	0.64	23.6 ± 5.7	27.1 ± 27.6	0.88
C_{12} (mg/L)	2.7 ± 2.2	1.4 ± 0.6	0.13	2.6 ± 1.3	1.4 ± 0.5	0.14	2.9 ± 1.3	2.4 ± 0.8	0.70
Dose-normalized C_{12} (mg/L/g)	6.9 ± 5.8	2.2 ± 1.0	0.06	3.8 ± 1.6	2.6 ± 1.0	0.25	4.0 ± 1.8	4.7 ± 1.9	0.76
T_{max} (h)	3.9 ± 2.3	3.7 ± 1.8	0.79	3.5 ± 1.4	4.0 ± 2.0	0.70	4.0 ± 4.2	3.3 ± 1.1	0.85
Free MPA concentration									
$AUC_{0\text{-}12}$ (μg·h/L)	302.6 (284.4–574.2)	266.2 (138.9–506.7)	0.37	484.0 (414.6–736.4)	323.0 (179.8–509.1)	0.40	453.8 (367.3–540.3)	288.3 (186.9–389.7)	0.67
Dose-normalized $AUC_{0\text{-}12}$ (μg·h/L/g)	1431.1 (396.3–1595.0)	460.2 (324.1–1000)	0.14	672.3 (655.7–1022.7)	625.8 (333.0–956.6)	0.63	630.3 (510.2–750.4)	547.7 (373.8–721.7)	0.67
C_0 (μg/L)	10.1 (7.3–20.5)	11.9 (10.3–18.3)	0.63	12.5 (11.4–12.9)	6.2 (4.6–10.9)	0.11	16.9 (10.6–23.3)	18.5 (14.3–22.6)	1.00
Dose-normalized C_0 (μg/L/g)	32.1 ± 19.7	26.6 ± 10.7	0.53	18.3 (17.8–18.8)	11.4 (8.6–21.5)	0.40	23.5 (14.7–32.4)	35.8 (26.5–45.2)	1.00
C_{max} (μg/L)	126.1 (88.1–160.3)	95.1 (22.9–199.0)	0.30	164.8 (162.3–274.6)	124.8 (51.1–468.7)	0.40	120.6 (88.2–153.1)	143.0 (39.5–246.4)	1.00
Dose-normalized C_{max} (μg/L/g)	351.4 ± 238.6	218.7 ± 207.2	0.30	305.1 (263.6–419.6)	242.3 (94.6–873.66)	0.86	167.6 (122.5–212.6)	267.6 (79.0–456.3)	1.00
C_{12} (μg/L)	15.1 (8.5–20.5)	10.5 (9.2–25.8)	0.73	13.2 (11.8–21.9)	6.2 (4.6–17.6)	0.23	16.9 (10.6–23.3)	16.6 (10.5–22.6)	0.67
Dose-normalized C_{12} (μg/L/g)	47.3 (14.0–94.4)	19.8 (18.0–41.5)	0.53	19.2 (18.8–30.8)	11.4 (8.6–34.9)	0.23	23.5 (14.7–32.3)	35.8 (26.5–45.2)	1.00
T_{max} (h)	3.3 ± 2.3	3.5 ± 1.8	0.84	2 (1.8–3)	5 (2–5.4)	0.40	4 (1–7)	3.5 (2.5–4.5)	1.00
Free MPA $AUC_{0\text{-}12}$/Total MPA $AUC_{0\text{-}12}$ (%)	0.9 (0.5–1.0)	0.9 (0.6–1.2)	0.71	0.8 (0.7–0.8)	0.8 (0.8–1.5)	0.63	0.7 (0.6–0.8)	0.7 (0.7–0.8)	1.00

*Data are presented as mean ± SD or median (interquartile range) for continuous variables and number and percentage for categorical variables.

†4–6 weeks postrandomization.

‡14–16 weeks postrandomization.

§28–32 weeks postrandomization.

¶Variables were compared using the *t*-test or Mann–Whitney *U*-test as appropriate, and dichotomous variables were compared using the Pearson χ^2 test or Fisher exact test as appropriate. Bold values indicate statistical significance ($P < 0.05$).

$AUC_{0\text{-}12}$, area under the concentration–time curve between 0 and 12 hours; C_0, predose concentration before EC-MPS administration; C_{12}, trough concentration at 12-hour post–EC-MPS administration; C_{max}, maximal MPA concentration; T_{max}, time when maximal MPA concentration is reached.

TABLE 3. Correlation Between Individual Sampling Timepoint With Total and Free MPA $AUC_{0–12}$

Sampling TimePoint for Total MPA Concentration (h)	Total MPA $AUC_{0–12}$ (mg·h/L) (n = 32)		Sampling Timepoint for Free MPA Concentration (h)	Free MPA $AUC_{0–12}$ (μg·h/L) (n = 24)	
	r*	*P*		r*	*P*
C_0	0.63	**<0.001**	C_0	0.53	**0.008**
C_1	0.63	**0.004**	C_1	0.48	**0.02**
$C_{1.5}$	0.63	**<0.001**	$C_{1.5}$	0.58	**0.006**
C_2	0.72	**<0.001**	C_2	0.56	**0.005**
$C_{2.5}$	0.68	**<0.001**	$C_{2.5}$	0.60	**0.002**
C_3	0.69	**<0.001**	C_3	0.48	**0.02**
$C_{3.5}$	0.63	**<0.001**	$C_{3.5}$	0.58	**0.003**
C_4	0.54	**0.002**	C_4	0.47	**0.02**
$C_{4.5}$	0.47	**0.01**	$C_{4.5}$	0.49	**0.02**
C_5	0.32	0.08	C_5	0.36	0.08
$C_{5.5}$	0.45	**0.01**	$C_{5.5}$	0.47	**0.02**
C_6	0.47	**0.01**	C_6	0.56	**0.006**
$C_{6.5}$	0.70	**<0.001**	$C_{6.5}$	0.72	**<0.001**
C_7	0.77	**<0.001**	C_7	0.40	0.07
C_8	0.88	**<0.001**	C_8	0.72	**<0.001**
C_{10}	0.72	**0.009**	C_{10}	0.71	**0.02**
C_{12}	0.60	**<0.001**	C_{12}	0.63	**0.001**

Bold values indicate statistical significance ($P < 0.05$). $AUC_{0–12}$, area under the concentration–time curve between 0 and 12 hours.
*Correlations between MPA concentrations and $AUC_{0–12}$ were evaluated by Pearson or Spearman correlation as appropriate.

in Centrifree regenerated cellulose 30,000 molecular weight cut-off centrifugal filter devices (Merck Millipore, Cork, Ireland) before centrifugation at ×3040*g* for 20 minutes at 37°C. The ultrafiltrate was then transferred to autosampler vials, mixed with MPA-d3 internal standard, and injected directly into the ultra-high performance liquid chromatography–tandem mass spectrometry system described previously. The assay was linear between 0.1 and 60 mg/L with intra-assay imprecision <4% and inter-assay imprecision <9%.

Outcome Measures

Primary

TDM of MPA was measured in CC and FD groups to determine whether TDM-guided dosing of EC-MPS resulted in achieving established targets of MPA AUC_{0-12} of 40–60 mg·h/L in participants receiving induction therapy and target AUC_{0-12} of 30–50 mg·h/L in participants receiving maintenance therapy compared with the standard empirical dosing in participants with LN.

Secondary

Secondary outcome measures were complete and partial remission rates in the induction group and sustained remission/renal relapse in the maintenance group.

Complete remission was defined as a decrease in urinary protein measured over 24 hours to less than 500 mg/24 hours, uPCR less than 0.5 mg/mg (50 mmol/mg), and normal serum albumin and stabilization (±25%) or improvement in serum creatinine levels at week 24 from the initial sample.[5] A partial remission was defined as stabilization (±25%) or improved renal function (but still not to normal) with reduction of proteinuria by more than 50% ranging between 300 and 3000 mg/24 hours and a serum albumin level of more than 30 g/L.[5] Renal relapse was defined as "recrudescence of renal disease after an initial response demonstrated by a recent increase in serum creatinine by >50% with active urinary sediment and/or increase in proteinuria to 3500 mg/d or greater."[15] Proteinuria was measured using uPCR or by 24-hour urinary protein excretion.

Statistical Methods

An interim analysis demonstrated slow recruitment, and the trial was terminated as most patients in the CC group achieved target AUC before intervention. Continuous data were compared using the Student *t*-test or Mann–Whitney *U* test as appropriate, and dichotomous variables were compared using the Pearson χ^2 or Fisher exact test as appropriate. Correlations between individual MPA concentrations and AUC_{0-12} for total and free drug concentrations were evaluated by Pearson or Spearman correlation as appropriate. All data were analyzed on an intention-to-treat basis, and a significance level of 0.05 was assumed. One of the coauthor, MHAA, who was masked to the study allocation and not involved in the clinical care of the participants adjudicated outcome measures.

RESULTS

Baseline Demographics and Clinical Characteristics

Twenty-seven patients were screened for eligibility, of whom 19 were randomly assigned to the FD (n = 9) or CC (n = 10) treatment groups. One participant was not compliant

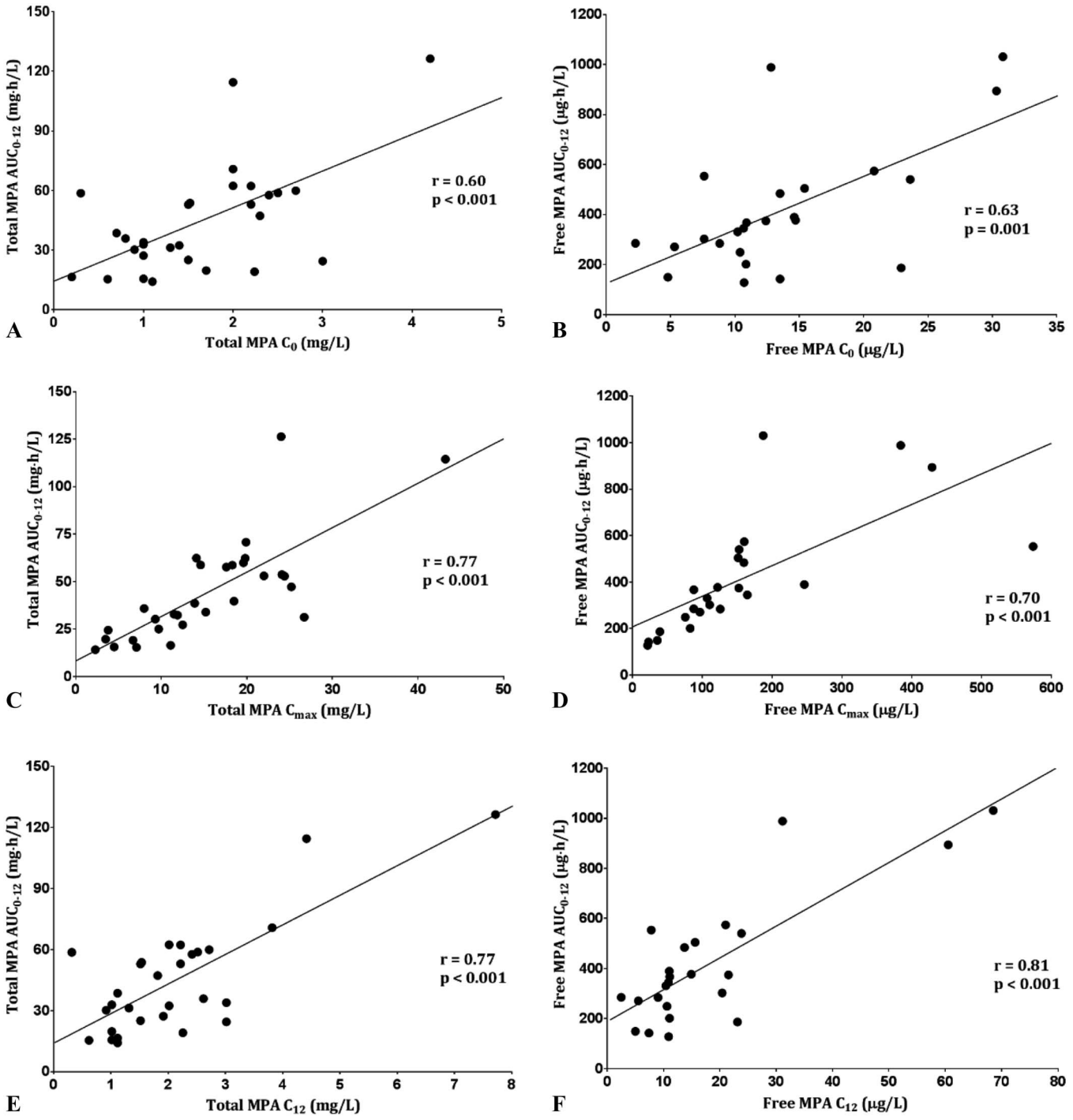

FIGURE 2. Correlations between MPA C_0 and MPA $AUC_{0\text{-}12}$ for (A) total MPA and (B) free MPA concentrations, between MPA C_{max} and $AUC_{0\text{-}12}$ for (C) total MPA and (D) free MPA concentrations, and between MPA C_{12} and MPA $AUC_{0\text{-}12}$ for (D) total MPA and (E) free MPA concentrations. $AUC_{0\text{-}12}$ = area under the concentration–time curve between 0 and 12 hours; C_0 = pre-dose concentration before EC-MPS administration; C_{max}, maximal MPA concentration C_{12}, trough concentration at 12-hour post–EC-MPS administration.

with treatment and was excluded from the outcome assessment. The final analysis only included 18 participants; 9 participants in each treatment group (Fig. 1).

The baseline characteristics of the 18 participants are presented in Table 1. There were no significant differences between FD and CC participants in any demographic and

TABLE 4. Achievement of Target MPA Exposure Range Between Fixed-Dosing and ConcentrationControlled Participants Stratified by the Study Visit

		Study Visit		
	Overall (n = 32)	**1***	**2†**	**3‡**
Participants with therapeutic MPA exposure, n (%)§				
Fixed-dosing	3 (20.0)	3 (33.3)	0 (0.0)	0 (0.0)
Concentration-controlled	9 (52.9)	1 (11.1)	5 (100.0)	3 (100.0)
P¶	0.06	0.58	**0.01**	0.10
Absolute difference (95% confidence interval)	0.32 (−0.57 to 0.00)	−0.22 (−0.17 to 0.55)	1.00 (−1.00 to −0.34)	1.00 (−1.00 to −0.14)

*Number of participants analyzed (4–6 weeks postrandomization): fixed-dosing = 9 and concentration-controlled = 9.
†Number of participants analyzed (14–16 weeks postrandomization): fixed-dosing = 4 and concentration-controlled = 5.
‡Number of participants analyzed (28–32 weeks post–randomization): fixed-dosing = 2 and concentration-controlled = 3.
§Target MPA exposure for participants receiving EC-MPS as induction therapy was 40–60 and 30–50 mg·h/L for maintenance therapy.
¶Comparisons were made using the Pearson χ^2 test or Fisher exact test as appropriate. Bold values indicate statistical significance ($P < 0.05$).
$AUC_{0\text{-}12}$, area under the concentration–time curve between 0 and 12 hours.

clinical characteristics at study entry. The mean (SD) follow-up time was 82.2 ± 33.3 weeks.

Mycophenolic Acid Pharmacokinetics

The total and free MPA pharmacokinetic parameters are summarized in Table 2. Thirty-two $AUC_{0\text{-}12}$ measurements were obtained from 18 participants; 18 AUCs from the first visit, 9 from the second visit, and 5 from the third visit. Large inter-patient variability (percentage coefficient of variation of ≥40%) was observed in all pharmacokinetic parameters across both groups, but these variations were more pronounced in the FD treatment group (percentage coefficient of variation of ≥60%). Correlations between MPA concentrations at different sampling time points, with $AUC_{0\text{-}12}$ for total and free MPA, are presented in Table 3. A moderate positive correlation was observed between MPA $AUC_{0\text{-}12}$ and C_0, C_{max} and C_{12} for total and free MPA concentrations (Fig. 2). Serum albumin inversely correlated with free C_{12} (r = −0.42; $P = 0.04$) and free MPA $AUC_{0\text{-}12}$ (r = −0.43; $P = 0.03$). There were no significant differences between FD and CC participants in any pharmacokinetic parameters across the study visits except for total C_0 (FD 2.0 ± 0.3 mg/L versus CC 1.1 ± 0.3; $P = 0.01$) and dose-normalized C_0 (FD 2.9 ± 0.2 mg/L/g versus CC 2.1 ± 0.7 mg/L/g; $P = 0.04$) at the second visit and total $AUC_{0\text{-}12}$ (FD 66.6 ± 6.0 mg·h/L versus CC 35.2 ± 11.4 mg·h/L; $P = 0.03$) at the third visit (Table 2).

Primary Outcome

The MPA exposure between FD and CC treatment groups across the 3 study visits is presented in Table 4 and Figure 3. Overall, 20.0% (n = 3/15) of FD participants and 52.9% (n = 9/17) of CC participants achieved the target MPA exposure range ($P = 0.06$). At the first study visit (week 4–6), only 33.3% (n = 3/9) of the FD participants and 11.1% (n = 1/9) of the CC participants achieved the target MPA exposure range ($P = 0.58$). However, from week 14, none of the FD participants achieved the target MPA exposure, whereas all the CC participants did. Nevertheless, a statistically significant difference between the 2 treatment groups was only observed on the second study visit (week 14–16) [FD 0.0% (n = 0/4) versus CC 100.0% (n = 5/5); $P = 0.01$]. Among those who failed to achieve the target exposure range (Fig. 4), 75% (n = 9/12) of the FD participants demonstrated supratherapeutic MPA exposure [mean ± SD (range) MPA exposure 57.9 ± 36.5 (1–126.3) mg·h/L].

Secondary Outcomes

Table 5 presents the differences in participant characteristics between those who demonstrated complete remission/sustained remission and partial remission in this study. At 24 weeks, 7 of the 9 FD participants (77.8%) and 5 of the 9 CC participants (55.6%) demonstrated either complete remission in the induction group or sustained remission in the maintenance group (absolute difference of −22.2, 95% confidence interval −0.19–0.55; $P = 0.62$). In this study, no participants had renal relapse in the maintenance group. There was no significant difference in the mean total MPA $AUC_{0\text{-}12}$ among participants who demonstrated complete and partial remission (37.8 ± 18.9 versus 49.6 ± 41.7 mg·h/L; $P = 0.32$). However, the mean free MPA $AUC_{0\text{-}12}$ was significantly lower in those who had complete remission than those with partial remission (311.6 ± 143.0 versus 631.8 ± 332.8 mg·h/L; $P = 0.01$). In this study, clinical response was not significantly associated with the achievement of target MPA exposure (Table 4).

Serum creatinine, blood urea, estimated glomerular filtration rate, serum albumin, and serum C3 and C4 were similar between FD and CC participants throughout the 48-week study period (Fig. 5).

Adverse Events

The total number of adverse events were similar between FD and CC treatment groups (Table 6). Nausea and vomiting as well as fever occurred in 2 patients for each group. The median (interquartile range) total MPA exposure of those participants with and without adverse events were 27.3 and 39.2 mg/L ($P = 0.11$), respectively. The median (interquartile range) free MPA exposure of participants with and without adverse events were 553.9 and 338.0 mcg/L,

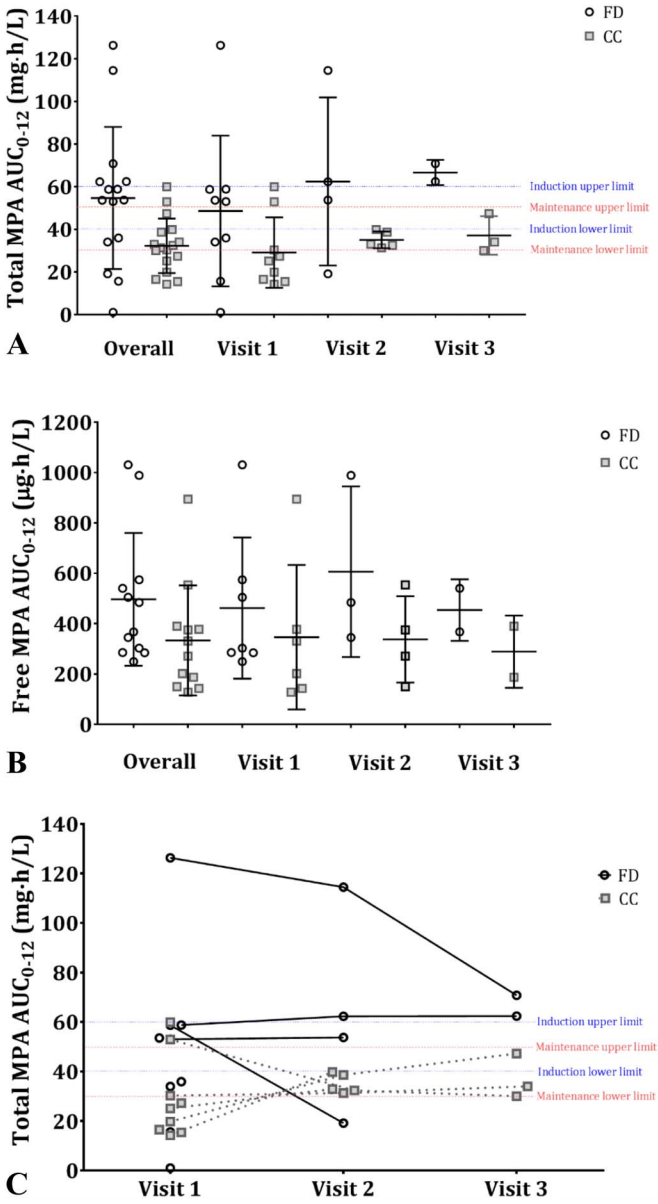

FIGURE 3. Total and free MPA $AUC_{0\text{-}12}$ between fixed-dosing and concentration-controlled participants across the study visits[a,b]. $AUC_{0\text{-}12}$, area under the concentration–time curve between 0 and 12 hours; CC, concentration-controlled; FD, fixed-dosing. [a]Mean with SDs are presented. [b]Dashed blue circles refer to the target MPA exposure range for patients receiving EC-MPS as induction therapy (40–60 mg·h/L) and dashed red lines refer to the target MPA exposure range for patients receiving EC-MPS as maintenance therapy (30–50 mg·h/L).

respectively ($P = 0.404$). Two participants in each treatment group had to discontinue EC-MPS due to treatment-related adverse events.

DISCUSSION

Our study is the first randomized controlled trial in LN patients to determine whether TDM-adjusted dosing achieved

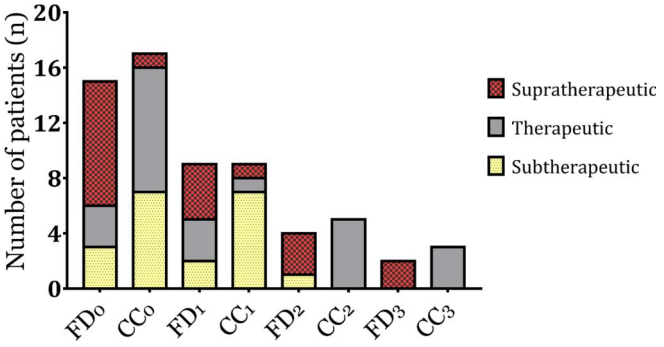

FIGURE 4. MPA exposure between fixed-dosing and concentration-controlled participants across the study visits[a,b,c]. [a]Target MPA exposure for participants receiving EC-MPS as induction therapy was 40–60 and 30–50 mg·h/L for maintenance therapy. [b]Subtherapeutic MPA exposure for participants receiving EC-MPS as induction therapy was defined as <40 and <30 mg·h/L for maintenance therapy. [c]Supratherapeutic MPA exposure for participants receiving EC-MPS as induction therapy was defined as >60 and >50 mg·h/L for maintenance therapy. FD_0, overall MPA exposure of FD participants; CC_0, overall MPA exposure of CC participants; FD_1, MPA exposure of FD participants on study visit 1; CC_1, MPA exposure of FD participants on study visit 1; FD_2, MPA exposure of FD participants on study visit 2; CC_2, MPA exposure of CC participants on study visit 2; FD_3, MPA exposure of FD participants on study visit 3; CC_3, MPA exposure of CC participants on study visit 3.

established MPA exposure targets efficiently compared with FD of EC-MPS. All CC participants reached target MPA exposure earlier than the FD group. The difference was statistically significant at the second study visit as EC-MPS dose was adjusted based on MPA exposure during the first visit.

The objective of CC dosing is to improve the clinical outcome and reduce adverse events with adequate drug exposure. MMF and EC-MPS are typically administered at a FD in patients with LN. There is wide interpatient variability of blood concentrations of MPA, the active metabolite of MMF, and EC-MPS. There are several studies on MMF dosing based on TDM attempting to improve outcome in LN, but there are little data on EC-MPS. Neuman et al were the first to show that the MPA exposure from EC-MPS is comparable in 12 autoimmune patients (mean 27.3 ± 17.4 mg/L) and 11 renal transplant patients (mean 19.6 ± 15.7 mg/L).[16] Lertdurrongluk et al studied the pharmacokinetics of MPA in 18 Thai patients with biopsy-proven LN, a month after initiating treatment with a FD of 1.0–1.5 g/D of MMF in 12 and 1080–1440 mg/D of EC-MPS in 6 patients, respectively.[11] The responders had a significantly higher MPA AUC (>45 mg·h/L). All these studies were either observational or retrospective, and the pharmacokinetics of MPA was studied after administering FD of MPA prodrugs.

A large inter-patient variability was observed in all pharmacokinetic parameters across both the groups as in other studies; however, this was more pronounced in the FD group. We observed a moderate correlation between MPA $AUC_{0\text{-}12}$ with C_0 and C_{max} for total and free MPA and a stronger correlation between MPA $AUC_{0\text{-}12}$ and C_{12}

TABLE 5. Differences in Clinical Characteristics and MPA Pharmacokinetic Parameters Between Participants Who Demonstrated Partial and Complete Remission at Week-24 Postrandomization*

Variable	Partial Remission (n = 6)	Complete Remission (n = 12)	*P*†
Age (in yr)	46.1 ± 16.2	50.8 ± 14.3	0.55
Sex, n (%)			
Male	2 (33.3)	2 (16.7)	0.57
Female	4 (66.7)	10 (83.3)	
Race, n (%)			
White	5 (83.3)	10 (83.3)	0.39
Asian	0 (0.0)	1 (8.3)	
Hispanic	0 (0.0)	1 (8.3)	
Others	1 (16.7)	0 (0.0)	
Weight (kg)	85.8 ± 21.3	74.5 ± 18.3	0.26
BMI (kg/m^2)	29.1 ± 6.0	26.4 ± 5.4	0.35
Renal pathology, n (%)			
ISN/RPS class III	0 (0.0)	4 (33.3)	0.26
ISN/RPS class IV	4 (66.7)	6 (50.0)	
ISN/RPS class V	2 (33.3)	2 (16.7)	
eGFR ($mL/min/1.73\ m^2$)	70.4 ± 45.3	86.1 ± 25.0	0.37
Urine protein (g/24 hours)	2.6 ± 1.9	0.3 ± 0.37	**0.02**
Urine protein/creatinine ratio	155.5 (88.8–296.0)	8.0 (6.3–24.8)	**<0.001**
Serum albumin (g/L)	31.5 ± 10.2	39.5 ± 3.3	**0.03**
Serum complement (g/L)			
C3	1.1 ± 0.3	1.0 ± 0.3	0.75
C4	0.2 ± 0.2	0.2 ± 0.1	0.43
Anti-dsDNA	54.5 ± 31.6	33.0 ± 41.8	0.30
EC-MPS dose (mg/d)	1350.0 (810.0–1620.0)	1440.0 (1080.0–1440.0)	0.81
Prednisolone dose (mg/d)	8.8 (4.4–23.8)	5.0 (5.0–10.0)	0.30
MPA pharmacokinetic parameters			
Total MPA concentration			
$AUC_{0\text{-}12}$ (mg·h/L)	49.6 ± 41.7	37.8 ± 18.9	0.32
Dose-normalized $AUC_{0\text{-}12}$ (mg·h/L/g)	77.8 ± 59.3	82.5 ± 70.7	0.88
C_0 (mg/L)	1.5 ± 1.1	1.5 ± 0.8	0.92
Dose-normalized C_0 (mg/L/g)	2.5 ± 1.5	3.4 ± 3.0	0.42
C_{max} (mg/L)	18.2 ± 12.4	13.9 ± 6.4	0.25
Dose-normalized C_{max} (mg/L/g)	28.2 ± 18.7	31.3 ± 30.0	0.80
C_{12} (mg/L)	2.4 ± 2.3	1.8 ± 0.8	0.36
Dose-normalized C_{12} (mg/L/g)	3.8 ± 3.2	4.3 ± 4.3	0.81
Free MPA concentration			
$AUC_{0\text{-}12}$ (μg·h/L)	631.8 ± 332.8	311.6 ± 143.0	**0.01**
Dose-normalized $AUC_{0\text{-}12}$ (μg·h/L/g)	1012.5 ± 383.1	731.9 ± 527.8	0.23
C_0 (μg/L)	12.1 (9.9–30.0)	10.4 (6.2–13.8)	0.44
Dose-normalized C_0 (μg/L/g)	24.2 (14.0–41.7)	19.5 (11.9–38.6)	0.76
C_{max} (μg/L)	273.0 ± 189.6	103.4 ± 51.5	**0.01**
Dose-normalized C_{max} (μg/L/g)	451.7 ± 317.1	252.7 ± 210.8	0.10
C_{12} (μg/L)	29.6 ± 25.0	10.9 ± 5.7	**0.02**
Dose-normalized C_{12} (μg/L/g)	45.3 ± 32.1	28.2 ± 28.9	0.24
Participants with therapeutic MPA exposure range, n (%)‡			
Overall	3 (33.3)	6 (33.3)	1.00
Therapeutic exposure on visit 1	1 (16.7)	3 (25.0)	1.00
Therapeutic exposure on visit 2	2 (66.7)	3 (50.0)	1.00

(*continued on next page*)

TABLE 5. (*Continued*) Differences in Clinical Characteristics and MPA Pharmacokinetic Parameters Between Participants Who Demonstrated Partial and Complete Remission at Week-24 Postrandomization*

Variable	Partial Remission (n = 6)	Complete Remission (n = 12)	P†
Treatment group, n (%)			
Fixed-dosing	2 (22.2)	7 (77.8)	0.62
Concentration-controlled	4 (44.4)	5 (55.6)	

*Data are presented as mean ± SD or median (interquartile range) for continuous variables and number and percentage for categorical variables.

†Continuous variables were compared using the *t*-test or Mann–Whitney *U*-test as appropriate, and dichotomous variables were compared using the Pearson χ^2 test or Fisher exact test as appropriate. Bold values indicate statistical significance ($P < 0.05$).

‡Target MPA exposure for participants receiving EC-MPS as induction therapy was 40–60 and 30–50 mg·h/L for maintenance therapy.

ALP, alkaline phosphatase; ALT, alanine transaminase; Anti-dsDNA, anti–double-stranded DNA; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; $AUC_{0\text{-}12}$, area under the concentration–time curve between 0 and 12 hours; BMI, body mass index; C_0, predose concentration before EC-MPS administration; C_{12}, trough concentration at 12-hour post–EC-MPS administration; C_{max}, maximal MPA concentration; EC-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; ISN/RPS, International Society of Nephrology/Renal Pathology Society.

total and free MPA concentrations in contrast to the lack of correlation reported by Lertdumrongluk et al[11] Djabarouti et al[17] studied TDM in 35 systemic lupus erythematosus patients with no renal involvement, 21 receiving MMF and 14 taking EC-MPS. They concluded, as we observed in our study with EC-MPS, that C12 after MMF ingestion could predict MPA AUC0-12. They, however, found the correlation to be weak in patients receiving EC-MPS.

We have shown earlier attainment of target AUC with lower doses using CC dosing in LN as compared with FD. This may be of importance with limiting side-effects in the longer term, especially in patients with a history of past immunosuppression or immune impairment and in regions where LN is more resistant to therapy. More CC participants achieved remission with lower doses compared with FD participants, although this difference did not reach statistical significance.

This is the first report to study the free MPA concentration on clinical outcome in LN patients treated with EC-MPS. Abd Rahman et al[18] studied the unbound fraction of MPA and its metabolite 7 -O-MPA-β-glucuronide (MPAG) in 25 LN patients receiving MMF. They found similar MPA exposure between responders and nonresponders. Our study also showed higher free MPA exposure in patients who had partial remission. Patients who had partial remission had lower albumin, resulting in higher free MPA exposure. We found an inverse correlation of albumin to MPA exposure in LN patients receiving EC-MPS.

This study has limitations with small sample size and premature termination due to slow recruitment. Despite these limitations, we observed that therapeutic exposure of MPA could be achieved with CC dosing. A larger study would define if CC dosing of EC-MPS improves therapeutic outcome in LN patients.

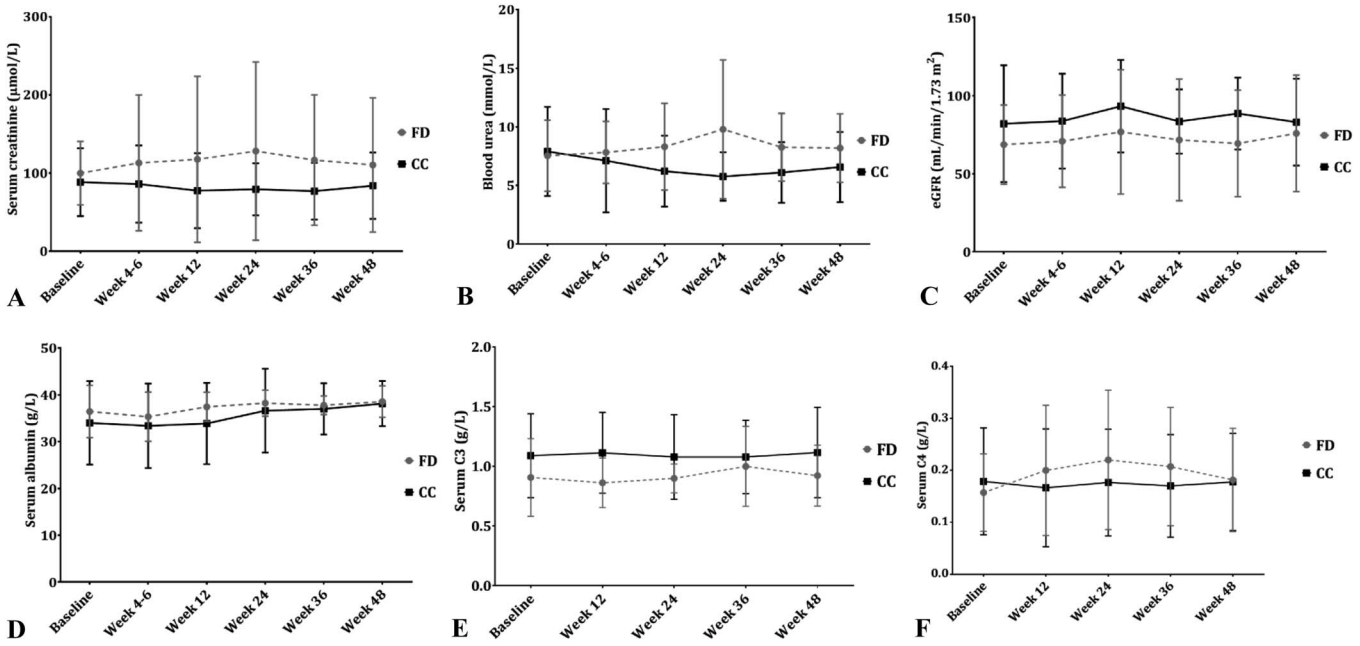

FIGURE 5. Changes in treatment-related variables over the 48 weeks of the study period[a]. FD, fixed-dosing; eGFR, estimated glomerular filtration rate. [a]No significant differences were observed in; (A) serum creatinine ($P = 0.33$), (B) blood urea ($P = 0.17$), (C) estimated glomerular filtration rate ($P = 0.95$), (D) serum albumin ($P = 0.68$), (E) serum C3 ($P = 0.35$), and (F) serum C4 ($P = 0.63$) between FD and CC participants throughout the study period.

TABLE 6. Adverse Events

Summary of Adverse Events, n (%)	Fixed-Dosing (n = 9)	Concentration-Controlled (n = 9)	*P*
Participants with ≥1 adverse event	1 (11.1)	1 (11.1)	1.00
Participants with adverse event leading to EC-MPS cessation	2 (22.2)	2 (22.2)	1.00
Total adverse events	5	7	0.32
Fever	1	1	
Infection	0	1	
Nausea & vomiting	1	1	
Others	3	4	

CONCLUSIONS

CC dosing of EC-MPS resulted in a higher proportion of participants achieving target exposure of MPA quicker. Larger prospective studies on CC drug dosing and therapeutic outcome will likely demonstrate the clinical efficacy of this approach.

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