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Comparison of Renal Responses Between Continuous Mycophenolate Mofetil and Conversion from Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium in Lupus Nephritis

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Background: Mycophenolate mofetil (MMF) is extensively used for induction and maintenance therapy in patients with lupus nephritis (LN). Enteric-coated mycophenolate sodium (EC-MPS) was developed to reduce the adverse gastrointestinal effects of MMF. However, the therapeutic efficacy of MMF and EC-MPS in LN remains unclear. This study aimed to examine the treatment effects of EC-MPS in LN patients with prior MMF exposure.

Methods: In this medical records review study, we included 54 LN patients, of whom 34 converted from MMF to EC-MPS at equimolar doses in 2016–2018 (nonmedical switching group) and 20 received continuous MMF treatment. Patients achieving complete remission or partial remission before the conversion were categorized as responders, whereas those who had never achieved complete remission or partial remission were categorized as nonresponders.

Results: Baseline proteinuria was higher in the nonmedical switching group. Although elevation in proteinuria was observed after nonmedical switching, the serum creatinine concentration and estimated glomerular filtration rate both improved. Responders in the nonmedical switching group had lower proteinuria and higher complement 3 levels. In the subgroup analysis, albeit the modest increase in daily urine protein, anti–double-stranded DNA antibody levels, estimated glomerular filtration rate, and complements 3 and 4 seemed comparable after conversion.

Conclusion: Switching to EC-MPS demonstrated a similar short-term renal response to continuous MMF treatment in LN patients. Prospective randomized trials are required to verify our findings.

Key Words: lupus erythematosus, lupus nephritis, mycophenolic acid

Lupus nephritis (LN), observed in approximately 50% of patients with systemic lupus erythematosus (SLE), is one of the most important predictors of overall mortality.[1] Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid (MPA), has been approved by the US Food and Drug Administration for prophylaxis of acute rejection in organ transplantation since 1995. In the late 1990s, MMF was introduced to manage relapsing or refractory LN previously treated with cyclophosphamide.[2] The first randomized prospective trial in 2000 utilizing MMF on Chinese patients with proliferative LN also demonstrated that the combination of prednisolone and MMF is as effective as the induction therapy of prednisolone and cyclophosphamide followed by prednisolone and azathioprine.[3]

The most common adverse effects of MMF are gastrointestinal events such as diarrhea, nausea/vomiting, and abdominal cramps.[4] Enteric-coated mycophenolate sodium (EC-MPS) was developed to ameliorate the gastrointestinal adverse effects associated with MMF. Prior studies demonstrated that patients suffering from the gastrointestinal adverse effects of MMF could benefit from switching to EC-MPS.[5,6] Moreover, previous trials with organ transplant patients demonstrated that EC-MPS was as safe and efficacious as MMF.[7,8] One phase III, randomized, double-blind multicenter study also demonstrated therapeutic equivalence in transplant patients being converted to EC-MPS.[9] However, randomized controlled trials comparing MMF and MC-MPS in LN patients are lacking. The therapeutic effects of conversion from MMF to EC-MPS in LN patients remain unclear.

In December 2016, the Taiwan Food and Drug Administration originally approved EC-MPS in LN treatment. Patients with biopsy-proven class III, IV, or V LN are eligible for reimbursement of EC-MPS. However, MMF had not been covered by the Taiwan Health Insurance for LN therapy in December 2016. The reimbursement differences provided an opportunity to investigate the effectiveness of nonmedical switching from MMF to EC-MPS. Our study aimed to evaluate the short-term treatment response of conversion from MMF to EC-MPS in patients with LN.

MATERIALS AND METHODS

Study Participants

Between December 2016 and September 2018, we conducted a longitudinal study of 50 LN patients who had been switched from MMF to EC-MPS by medical record reviews. All the participants

are Han Chinese in ethnicity. Patients younger than 20 years and those undergoing renal replacement therapy were excluded. We excluded patients with MMF administered for less than 12 months before the conversion to EC-MPS. Nine subjects among whom MMF had been prescribed for less than 12 months before switching to EC-MPS were excluded. Further, we excluded 7 subjects with a short duration of EC-MPS (<12 months). Finally, 34 patients with nonmedical switching were analyzed in this study, with the index day when they switched into EC-MPS.

Furthermore, we selected 20 LN patients receiving continuous MMF treatment with the minimum use of 12 months before the index day (January 1, 2017) as the reference group. After the index day, the continuous treatment group kept MMF treatment because of good tolerance to MMF. The diagnosis of SLE met the 1997 American College of Rheumatology classification criteria for lupus.[10] Systemic lupus erythematosus patients were determined using the *International Classification of Diseases, Ninth Edition, Clinical Modification* code 710.0 and *International Classification of Diseases, Tenth Edition, Clinical Modification*: M32.0–M32.9.

The MMF dose was started at 0.5 g/d and reached a maximum of 2 g/d.[11] At the time of conversion, the initial dose of EC-MPS was divided into 2 doses that were administered equimolarly to that of MMF (360 mg of EC-MPS for 500 mg of MMF).

Data Source

The data analyzed in this study were acquired from the Oracle Hyperion system utilized at Taichung Veterans General Hospital. All inpatient and outpatient data were anonymized before the analysis to protect patients' privacy. This study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Taichung Veterans General Hospital (CE18210B).

Clinical Assessment

Data were collected on the index day and 2 follow-up points: 3 months before and after the index day. Index day for the continuous MMF group was January 1, 2017; for the nonmedical switching group, it was the day of conversion from MMF to EC-MPS. Laboratory measurements included urine protein-to-creatinine ratio (UPCR), serum creatinine, estimated glomerular filtration rate (eGFR), anti–double-stranded DNA antibodies (anti-dsDNA ab), complement 3 (C3), and complement 4 (C4).

Renal Remission Criteria

Complete remission (CR) was defined as proteinuria <0.5 g/d and normal or near-normal renal function. Partial remission (PR)

TABLE 1. Patient Characteristics of Nonmedical Switching and Continuous MMF Treatment Groups

	Continuous MMF (n = 20)		Nonmedical Switching (n = 34)		
	Median or n	Range or %	Median or n	Range or %	*p* value
Age, y	38	21–61	35	16–60	0.462
Female	16	80.0%	27	79.4%	1.000
Disease duration,[a] y	8.4	3.1–13.2	6.4	1.3–12.4	0.142
Prior nephrotic flares[a]	4	20.0%	19	55.9%	0.022[b]
Duration of MMF therapy,[a] y	4.5	0.6–10.4	4.8	0.9–10.5	0.567
UPCR, mg/mg	0.20	0.04–4.47	0.99	0.08–6.73	0.001[c]
Serum creatinine, mg/dL	0.80	0.59–2.74	0.90	0.5–3.87	0.503
eGFR, mL/min per 1.73 m^2	96.3	22.4–118.8	84.2	13.0–137.2	0.440
Anti-dsDNA ab, WHO U/mL	117.2	11.2–382.9	68.1	7.2–470.2	0.470
C3, mg/dL	91.6	40.1–154	89.4	30.9–128.4	0.463
C4, mg/dL	16.0	6.2–33.4	18.8	1.1–48.1	0.970
Renal histopathology					0.145
III	5	25.0%	6	17.6%	
III + V	0	0%	3	8.8%	
IV	12	60.0%	18	52.9%	
IV + V	0	0%	2	5.9%	
V	3	15.0%	1	2.9%	
Not biopsied	0	0%	4	11.8%	
Concomitant medications					
Daily prednisolone dose, mg	10.0	0–40	9.6	0–40	0.621
HCQ	18	90.0%	32	94.1%	0.622
CsA	3	15.0%	5	14.7%	1.000
AZA	2	10.0%	3	8.8%	1.000
CYC pulse for LN induction	6	30.0%	16	47.1%	0.345
Subsequent nephrotic flares[d]	0	0%	12	35.3%	0.002[b]

[a]Disease duration, nephrotic flares, and duration of MMF therapy prior to the index day (for the continuous MMF group: January 1, 2017; for the nonmedical switching group, the date of conversion to EC-MPS).

[b]$p < 0.05$.

[c]$p < 0.01$.

[d]Subsequent nephrotic flares indicate the occurrence of nephrotic-range proteinuria between the index day and October 31, 2019.

AZA, azathioprine; CYC, cyclophosphamide; CsA, cyclosporine; HCQ, hydroxychloroquine.
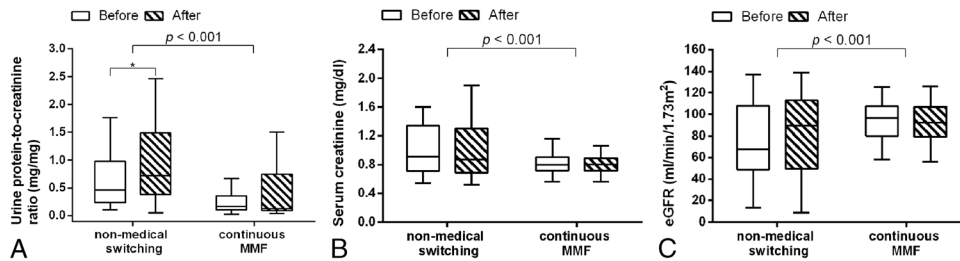
FIGURE. Comparisons of (A) UPCR, (B) serum creatinine concentration, and (C) eGFR of responders in the nonmedical switching and continuous MMF treatment groups by GEE. Laboratory data were collected 3 months before and after the index day. *$p < 0.05$.

was defined as proteinuria reduction by ≥50% and normal or near-normal GFR.[12] For analysis, enrolled participants were stratified into responders and nonresponders. Responders were defined as those who had achieved CR or PR when switching to EC-MPS. Patients who had never achieved PR were defined as nonresponders. The primary outcome was the response rate at 3 months after conversion to EC-MPS.

Renal Histopathology

A kidney biopsy was performed before the index day unless patients exhibited contraindications (e.g., bleeding tendency or small kidney size). The classification of LN was defined according to the 2003 International Society of Nephrology/Renal Pathology Society criteria.[13]

Statistical Methods

Data are presented as median and range. The Mann-Whitney U test and Fisher exact test were used to compare the MMF and nonmedical switching groups and to examine the differences between the responder and nonresponder groups. The response rate after the conversion to EC-MPS was performed by Fisher exact test. Wilcoxon signed ranks test was utilized to compare clinical parameters before and after conversion from MMF to MC-MPS by genders and renal histology patterns. We used the generalized estimating equations (GEEs) to compare laboratory data between the responders of the nonmedical switching group and those of the continuous MMF treatment group. All data were analyzed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY). Statistical significance was set at $p < 0.05$.

RESULTS

Table 1 displays patient demographics and renal histopathology of 34 patients receiving nonmedical switching and 20 patients with continuous MMF treatment. Higher proteinuria levels were observed in the nonmedical switching group ($p = 0.001$). Class IV LN was the most frequent renal histologic pattern in both groups. Gastrointestinal adverse events were observed in 6 patients (17.6%) in the nonmedical switching group (2 with diarrhea, 2 nausea/vomiting, and 2 abdominal cramps). Before the index day, renal flares with nephrotic-range proteinuria were more frequent in the nonmedical switching group (20.0% vs. 55.9%, $p = 0.022$). The median follow-up time after the nonmedical switching was 713 days (interquartile range, 681–779 days), and the median for the continuous MMF treatment group was 2953 days (interquartile range, 2060–3852 days). Nephrotic flares had developed in 12 patients (35.3%) of the nonmedical switching group. In contrast, none in the continuous MMF group had nephrotic flares after the index day ($p = 0.002$).

TABLE 2. Patient Characteristics of MMF Responders and Nonresponders in the Nonmedical Switching Group

	Nonresponder (n = 3)		Responder (n = 31)		Total (n = 34)		
	Median or n	Range or %	Median or n	Range or %	Median or n	Range or %	*p* value
Age, y	35	30–36	35	16–60	35	16–60	0.918
Female	3	100	24	77.4%	27	79.4%	1.000
UPCR, mg/mg	3.20	2.42–6.73	0.95	0.08–4.25	0.99	0.08–6.73	0.008[a]
Serum creatinine, mg/dL	0.90	0.79–1.00	0.89	0.50–3.87	0.9	0.50–3.87	0.965
eGFR	95.2	60.8–117.8	76.0	13.0–137.2	84.2	13.0–137.2	0.635
Anti-dsDNA ab, WHO U/mL	72.2	66.5–449.9	57.6	7.2–470.2	68.1	7.2–470.2	0.315
C3, mg/dL	46.6	30.9–59.9	90.9	46.1–128.4	89.4	30.9–128.4	0.006[a]
C4, mg/dL	2.2	1.1–22.2	19.3	5.1–48.1	18.8	1.1–48.1	0.144
Renal histopathology							0.764
III	0	0%	6	19.4%	6	17.7%	
III + V	0	0%	3	9.7%	3	8.8%	
IV	2	66.7%	16	51.6%	18	52.9%	
IV + V	0	0%	2	6.5%	2	5.9%	
V	0	0%	1	3.2%	1	2.9%	
Not biopsied	1	33.3%	3	9.7%	4	11.8%	

[a]$p < 0.01$.

In the MMF treatment group, 18 patients had achieved either PR or CR before the index day, and 2 patients were nonresponders. In the nonmedical switching group, 3 were categorized as MMF nonresponders and 31 were MMF responders before being converted to EC-MPS. We compared the renal responses of both groups' responders in the 3-month interval after the index day. All responders in the continuous MMF treatment group remained in either CR or PR in the 3-month follow-up after the index day. Among the 31 responders in the nonmedical switching group, only 1 patient became a nonresponder. We analyzed UPCR, serum creatinine, and estimated GFR at a 3-month interval from the responders in both groups (Figure). We observed a modest increase in the UPCR after nonmedical switching compared with the continuous MMF treatment ($p < 0.001$ by GEE, Fig. A). In contrast, a slight decline in serum creatinine level was noted after being switched to EC-MPS that corresponded with a moderate increment in eGFR compared with the persistent MMF group ($p < 0.001$, respectively, by GEE, Figs. B and C).

Table 2 shows the baseline patient demographics of the nonmedical switching group. As expected, the UPCR was significantly higher in the nonresponder subgroup than in the responder subgroup ($p = 0.008$). We found that despite comparable levels of anti-dsDNA ab and C4, MMF nonresponders exhibited significantly lower C3 levels compared with MMF responders ($p = 0.006$). Among both nonresponders and responders, class IV was the most common pathological class of LN.

We analyzed the response rates at 3 months after conversion to EC-MPS. Two patients in the nonresponder group achieved renal response (66.7%), and 1 patient (33.3%) still lacked any treatment response after switching from MMF to EC-MPS. Meanwhile, 30 initial MMF responders (96.8%) still exhibited good responses to EC-MPS, whereas 1 patient (3.2%) became a nonresponder after switching to EC-MPS.

To investigate whether clinical parameters might change after switching by gender and renal pathology classification, we compared UPCR, serum creatinine, eGFR, anti-dsDNA ab, and complement levels at 3 months before and 3 months after the conversion to EC-MPS (Supplementary Table, http://links.lww.com/RHU/A345). We observed a modest increase in the UPCR after switching ($p = 0.008$). The increased urinary protein after conversion was found only in females. Moreover, we observed decreased anti-dsDNA ab levels after switching from MMF to EC-MPS, particularly in female patients ($p = 0.016$, Supplementary Table) and patients with LN class III or IV ($p = 0.012$, Supplementary Table).

DISCUSSION

In our study, despite a slight increase in UPCR after switching, renal function tests and serologic markers for SLE remained stable; therefore, the observation of similar effectiveness between MMF and EC-MPS may shed light on EC-MPS utilization in treating patients with LN. Previous reports regarding switching from MMF to EC-MPS in renal transplant patients demonstrated that the 2 drugs exhibited therapeutic equivalence. Similar rates of efficacy failure and rejection were observed in both groups.[9] However, whether EC-MPS is effective among LN patients refractory to MMF remains uncertain. In our study, we observed similar responses to EC-MPS in prior MMF responders. Renal function and serologic markers for lupus activity remained unchanged. However, slightly increased urinary protein was observed at 3 months in female LN patients after conversion. This result could be related to more severe renal involvement in female participants because all 3 MMF nonresponders were female. It might take a more extended period for female patients to achieve CR or PR after conversion from MMF to EC-MPS. Moreover, despite the increased UPCR, anti-dsDNA ab levels conversely decreased; complement levels were also similar after nonmedical switching.

The present study has several limitations. First, this was a chart review study. Our result could be biased because patient characteristics in both groups were not equally distributed. Second, the present study contains no analysis of the disease severity of SLE, histologic activity, and chronicity scores; thus, whether the histopathologic characteristics of renal biopsy can predict the effectiveness of conversion from MMF to EC-MPS remains unknown. Third, the induction therapy for each LN participant was not taken into consideration. We cannot exclude potential bias because of the use of various induction regimens in our cohort. Fourth, severe infection rates before and after conversion to EC-MPS were not prospectively collected in this study. Previous reports in transplant patients showed lower serious infection rates in the EC-MPS group compared with their counterparts.[9] Fifth, all the study participants are Han Chinese. Our results may not be extrapolated to population with non-Asian genetic background. Finally, all participants in this study were nonmedically switched from MMF to EC-MPS because of a change in health insurance reimbursement; our results might not be applicable to other LN populations.

CONCLUSION

Switching from MMF to EC-MPS can be an option when treating LN. Switching to EC-MPS demonstrated similar short-term renal response compared with continuous MMF treatment in LN patients. Prospective studies with larger sample sizes are required to examine the long-term effectiveness and safety profile of conversion from MMF to EC-MPS.

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