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Original Article

Comparison of mycophenolic acid with cyclophosphamide for the treatment of pediatric lupus nephritis: A retrospective study from a tertiary center hospital in Taiwan

Huei-Geng Chen [a,b], Jin-Shuen Chen [c], Yao-Shen Chen [c], Chun-Hao Yin [d,e], Hsiao-Ching Chen [a], Yee-Hsuan Chiou [a,f,g,*]

[a] *Division of Pediatric Allergy Immunology and Rheumatology, Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[b] *Department of Pediatrics, Tainan Municipal Hospital (Managed by Show Chwan Medical Care Corporation), Tainan, Taiwan*
[c] *Department of Administration, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[d] *Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[e] *Institute of Health Care Management, National Sun Yat-sen University, Taiwan*
[f] *Division of Pediatric Nephrology, Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[g] *Department of Medical Laboratory Science and Biotechnology, Fooyin University, Kaohsiung, Taiwan*

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Abstract *Background:* This study aimed to compare the efficacy of mycophenolic acid (MPA) and cyclophosphamide (CYC) for treating pediatric lupus nephritis (pLN).
Methods: Data on patients with pLN class III, IV, and V, diagnosed by renal biopsy, were collected from the Databank of Kaohsiung Veterans General Hospital between February 2005 and December 2020. The study included 31 pLN patients. Of these, 15 received MPA (MPA group) and 16 received CYC (CYC group). Systemic lupus erythematosus disease activity index score, laboratory findings, complete remission (CR), and partial remission (PR) were assessed at 6, 12, and 24 months.
Results: In the MPA group, CR occurred in 7/15 (47%) patients at month 6 and in 11/15 (73%) at months 12 and 24. In the CYC group, CR was reached in 5/16 (31%) patients at month 6, in 8/16

* Corresponding author. Department of Pediatrics, Kaohsiung Veterans General Hospital, No.386, Dazhong 1st Rd., Zuoying Dist., Kaohsiung City 81362, Taiwan.
E-mail address: chysn@ms6.hinet.net (Y.-H. Chiou).

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(50%) at month 12, and in 9/16 (56%) at month 24. PR was seen in 3/15 (20%) patients in the MPA group and in 3/16 (19%) in the CYC group at month 24. The cumulative probability of CR and PR showed no statistically significant difference between the two groups. However, the estimated glomerular filtration rate (eGFR) improved significantly in the MPA group at months 6, 12 and 24 compared to that in the CYC group ($p < 0.05$).
Conclusion: The efficacy of MPA is similar to that of CYC for pLN treatment, with MPA providing a significant improvement in eGFR after pLN induction therapy at months 6,12 and 24.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that can involve almost any organ of the body, including kidneys where it can cause lupus nephritis (LN). The incidence of childhood-onset SLE (cSLE) is 0.36—2.5 per 100,000 children per year and the prevalence is 1.89—25.7 per 100,000 children worldwide.[1] In Taiwan, the prevalence of cSLE is 6.3 per 100,000.[2] It has been reported that 50—75% of cSLE patients will develop renal involvement, of which >90% will develop renal disease within 2 years of cSLE diagnosis.[3] LN manifests with more frequent and severe symptoms in pediatric patients than adult patients and is also associated with high morbidity and mortality rates.[3,4] In adults, end-stage kidney disease (ESKD) due to LN has a particularly poor prognosis.[5] Hiraki et al. reported a 5-year mortality rate of 22% after patients with LN received renal replacement therapy.[6]

Due to the poor outcome of pediatric LN (pLN), appropriate therapy is essential. According to recent guidelines for LN treatment, the regimen of National Institute of health (NIH), CYC is given 750 mg/m^2 monthly for 6 months as induction therapy, and MMF is given 2—3 g/day for 6 months as induction therapy. In this study, after the first 6 months of induction therapy, the patient received maintenance therapy for 1.5 years.[7—10] CYC has been used to treat LN for over 20 years, but adverse effects such as ovarian insufficiency in females, infertility, and long-term gonadal damage in males have been reported.[11]

Mycophenolic acid (MPA) is a selective inhibitor of the *de novo* synthesis of guanosine nucleotides, inhibiting lymphocyte proliferation, which helps to stop the inflammation process.[12] MPA has a more favorable toxicity profile than CYC, having minimal impact on other tissues with high proliferative activity that possess a salvage pathway for nucleotide synthesis.[13] There are two forms of MPA drugs: mycophenolate mofetil (MMF) and myfortic acid (enteric-coated mycophenolate sodium). MMF is a morpholino ester prodrug of MPA and causes less bone marrow suppression as its preferred target is activated lymphocytes.[14] MMF has been proven as an effective therapy for LN as an induction and maintenance treatment.[15] The adverse effects of MMF are mainly gastrointestinal disturbances. Myfortic acid has been developed as an advanced formulation delivering the bioequivalent MPA dose as MMF, and was approved for transplant recipients, particularly for those with gastrointestinal intolerance to MMF.[16—18]

Considering that most pLN patients are either at prepubertal or pubertal age, the adverse effects of CYC are a major concern. A meta-analysis by Jiang et al. revealed that the frequency of menstrual abnormalities in the MMF group was lower than that in the CYC group, and MMF was thus a better therapy for adolescent or patients of reproductive age with LN.[14] The study indicated that LN patients, especially at pre-pubertal or pubertal age, could select medicines with less adverse effects for LN treatment.

To our knowledge, no other study has compared the outcomes of CYC and MPA in treating pLN in Taiwan. Therefore, we conducted a retrospective study to analyze the outcomes after different induction therapies of pLN.

Methods

We conducted a retrospective analysis of pediatric patients (<18 years old) with cSLE at Kaohsiung Veterans General Hospital (KSVGH), a tertiary referral center in southern Taiwan, between February 2005 and December 2020. For the precise enrollment of study cases, we used the International Classification of Diseases, the Ninth Revision (ICD-9)-Clinical Modification code 710.0, or the Tenth Revision (ICD-10)-Clinical Modification code M32.10 with Clinical Modification codes M32.1—32.9, to obtain information and these patients received a catastrophic illness certification approved by the National Health Insurance (NHI) program of Taiwan. The catastrophic illness certification of SLE is prescribed strictly by doctors when patients fulfill the 1997 American College of Rheumatology Revised Criteria for Classification of SLE.[19] Among the cases with catastrophic illness certification, the enrolled patients have kidney biopsy before 2020/12, and the biopsy result is pLN. Of the pLN cases proven by kidney biopsies, only class III, IV, and V patients with complete treatment of either MPA or CYC were enrolled. LN was classified according to the World Health Organization.[20,21] The exclusion criteria included patients who received incomplete treatment, such as patients who visited outpatient department once without any subsequent visits, developed ESKD within 3 months without receiving induction therapy. All study cases were classified into MPA and CYC groups. Medical records were reviewed, and all confirmed cases received LN therapy based on the guidelines of the NIH.[7—10]

In the CYC group, intravenous CYC was administered at a dose of 500—1000 mg/m^2 monthly for 6 months as induction therapy, followed by administration every 3 months for the next 18 months as maintenance therapy. In the MPA group, MPA was administered for 6 months as induction therapy. MPA drugs included MMF and myfortic acid, with MMF

Table 1 Demographic and clinical characteristics at pre-induction of two groups with pediatric lupus nephritis.

	Total	MPA group	CYC group	
	n = 31	n = 15	n = 16	*p* value
Diagnostic SLE age (years)	13.9 (12.2–16.1)	13.2 (12.2–14.4)	14.3 (11.6–16.7)	0.379
Diagnostic Lupus nephritis age (years)	14.1 (12.1–16.8)	14.1 (12.1–17.6)	14.2 (11.7–16.7)	0.740
Gender				
Male	5 (16.1)	3 (20.0)	2 (12.5)	0.654
Female	26 (83.9)	12 (80.0)	14 (87.5)	
Height (cm)	155 (148.0–160.0)	155.0 (153.0–160.0)	154.0 (145.1–160.0)	0.470
Body weight (kg)	48.0 (39.5–55.2)	48.0 (40.3–56.4)	48.0 (38.6–52.7)	0.470
BMI (kg/m^2)	19.0 (17.4–21.2)	18.9 (17.0–21.9)	19.8 (17.9–21.2)	0.654
Histopathological classification				
III	1 (3.2)	1 (6.7)	0 (0.0)	0.725
IV	21 (67.7)	9 (60.0)	12 (75.0)	
V	2 (6.5)	1 (6.7)	1 (6.3)	
IV + V	3 (9.7)	1 (6.7)	2 (12.5)	
III + V	4 (12.9)	3 (20.0)	1 (6.3)	
WBC (K/uL)	7.3 (4.3–11.3)	6.6 (4.3–9.8)	9.1 (4.5–14.7)	0.470
Hemoglobin (Hb, g/dL)	10.2 (8.6–11.3)	10.0 (8.5–10.6)	10.3 (8.7–12.3)	0.567
Platelet count (K/uL)	235.5 (156.0–282.0)	253.0 (209.0–271.0)	211.5 (137.3–306.5)	0.379
Serum creatinine (mg/dL)	0.9 (0.6–1.2)	0.8 (0.6–1.1)	0.9 (0.8–1.7)	0.188
Serum albumin (g/dL)	2.9 (2.5–3.4)	3.3 (2.7–3.7)	2.8 (2.5–3.3)	0.119
GPT (U/L)	19.8 (11.8–32.3)	18.3 (9.5–32)	22.0 (12.4–36.3)	0.423
TG (mg/dL)	194.5 (112.5–271.3)	175 (94.5–266)	208.0 (142.5–296.5)	0.401
Anti-ds DNA (IU/ml)	304.7 (25.0–1617.5)	650.0 (48.3–2251)	107.0 (25.0–1440.3)	0.449
C3 (mg/dL)	41.9 (24.1–58.3)	44.7 (23.8–70.2)	39.4 (27.2–56.8)	0.953
C4 (mg/dL)	8.7 (5.3–12.3)	11.6 (5.3–13.9)	8.3 (3.5–11.7)	0.401
SLEDAI score	18.0 (13.0–21.0)	14.0 (8.0–22.0)	18.0 (16.0–20.0)	0.358
eGFR (mL/min/1.73 m^2)	72.3 (55.1–97.2)	89.3 (59.1–105.1)	69.4 (39.7–77.6)	0.163
Proteinuria (mg/day)	1641.2 (489.0–4556.3)	1506.6 (700.2–5866.6)	1787.5 (325.8–4632.5)	0.880
Urine (patient numbers)				
Hematuria	16 (51.6)	7 (46.7)	9 (56.3)	0.724
non-Hematuria	15 (48.4)	8 (53.3)	7 (43.8)	

Continuous variables were presented by median (Q1-Q3) and Mann-Whitney U test.
Categorical variables were presented by number (%) and Fisher's exact test.
Significant level: $p < 0.05$*, $p < 0.01$**, $p < 0.001$***.
CYC, Cyclophosphamide; MPA, Mycophenolic acid; SLE, Systemic lupus erythematosus; BMI, Body Mass Index; WBC, White blood cells count; GPT, Glutamic pyruvic transaminase; TG, Triglyceride; Anti-ds DNA, Anti-double stranded DNA antibody; C3, Complement factor 3; C4, Complement factor 4; SLEDAI, Systemic lupus erythematosus disease activity index; eGFR, estimated glomerular filtration rate; eGFR calculated using the New Schwartz formula.

administered twice a day at 300–600 mg/m^2 (maximum dose of 3 mg/day). It has been previously shown that 720 mg of myfortic acid is bioequivalent to 1000 mg of MMF when evaluating MPA exposure.[18] After the induction therapy, patients of MPA group received maintenance therapy with either azathioprine (2–2.5 mg/kg/day) or MPA (MMF 300–600 mg/m^2/dose twice daily, with a total dose of 1–2 gm/day, or myfortic acid in bioequivalent dose) for 1.5 years.[22] Both groups of patients received concomitant pulse corticosteroid therapy with methylprednisolone at 10–30 mg/kg (maximum dose 1 gm/day) monthly for 3–6 months, followed by oral prednisolone at a dose of 1 mg/kg/day to a maximum dose of 60 mg/day. Oral prednisolone was tapered over the following 6–8 weeks to a dose of 0.5 mg/kg/day.

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (IRB No. VGHKS20-CT12-14).

Measurements

Baseline demographic data of both groups are shown in Table 1. Clinical laboratory data for analysis were collected at the time of renal biopsy and pre-induction treatment (at month 0), including white blood cell count (WBC), hemoglobin (Hb) level, platelet count (PLT), serum creatinine level, serum albumin level (ALB), and glutamic pyruvic transaminase (GPT) level. Additionally, levels of anti-double stranded DNA antibody (anti-dsDNA), complement level (C3 and C4), and systemic lupus erythematosus

disease activity index (SLEDAI) score were compared. Estimated glomerular filtration rate (eGFR),[23] 24-h urine protein (proteinuria was defined as more than 500 mg of protein in a 24-h urine specimen) and the patient number of hematuria (hematuria was defined as >5 red cells per high power-field) were also included in Table 1.

The primary endpoint was complete remission (CR), and the secondary endpoint was partial remission (PR). Renal outcome was classified into three categories. CR was defined as no active clinical symptoms, a urine protein and creatinine ratio (UPCR) < 0.2, or daily proteinuria $\leq$0.5 g/day or sequential urine protein (UP) $< +1$. PR was defined as no clinical symptoms and as presenting a $\geq$ 50% improvement in UPCR (with maximum spot protein/creatinine ratio $\leq$1.0) or a decrease in daily proteinuria of $\geq$ 50% and daily proteinuria within 0.5—2.9 g/day, or sequential UP $\leq +2$. No-response (NR) was defined as a <50% improvement in UPCR or a decrease in daily proteinuria of <50% and daily proteinuria >3 g/day, or sequential UP $\geq +3$. Renal outcome was assessed at months 6, 12, and 24.

Statistical analysis

Demographic and clinical characteristics were summarized for the entire study population, divided into the MPA and CYC groups, and expressed as Median (Q1-Q3) or number (percentage). Differences between the MPA and CYC groups were calculated using the independent Mann—Whitney U test and χ2-test or Fisher's exact test for continuous and categorical variables, respectively. Wilcoxon sign rank test was employed to compare differences within groups. All statistical analyses were performed using Statistical Analysis Software (SAS; version 9.4; SAS System for Windows) and SPSS (version 20; SPSS Inc., Chicago, Illinois, USA). A p value of <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics at month 0

A total of 265 patients under 18 years of age were diagnosed with cSLE (Fig. 1). 210 cSLE patients without pLN were excluded from the study. A further 24 patients were excluded due to not receiving the complete 6-month treatment, where 6 patients with ESKD within 3 months, 9 patients not receiving MPA or CYC, and 9 patients visiting outpatient department only once. As a result, a total of 31 pLN patients with renal biopsy identified as class III, IV, and V were enrolled in our study. These patients were divided into two groups based on their induction therapies: 15

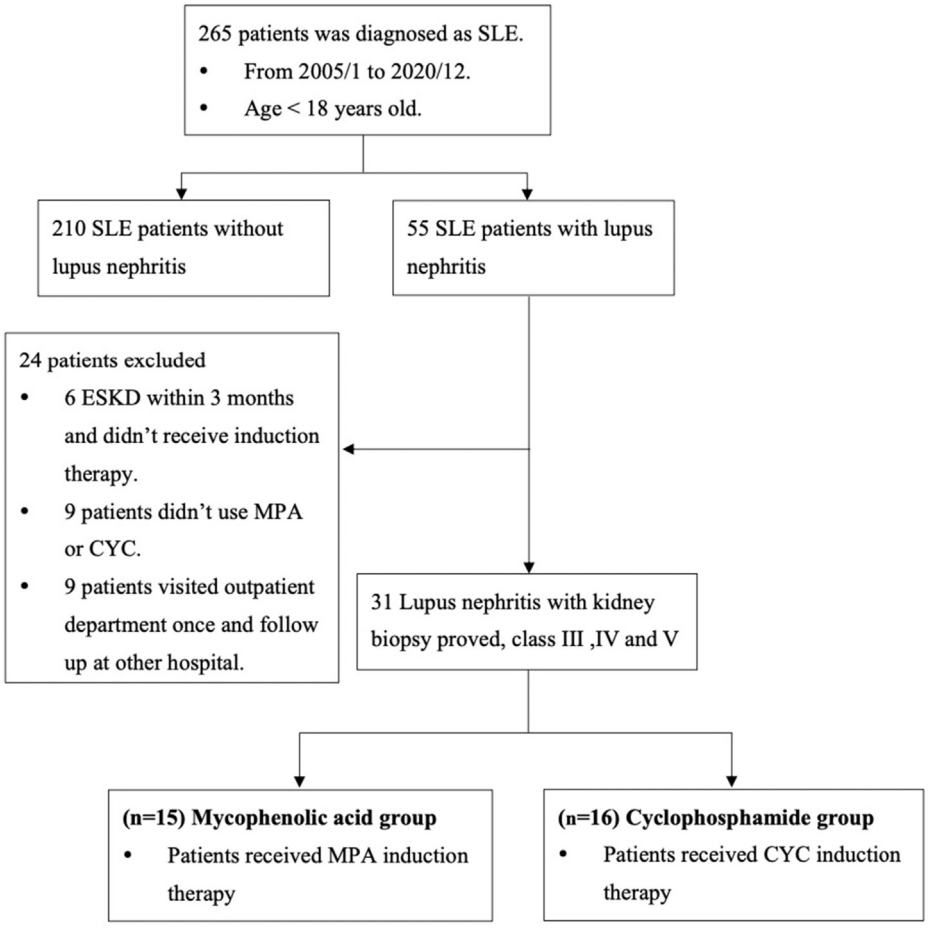


Figure 1. Flowchart depicting patient enrollment. SLE, Systemic lupus erythematosus; LN, lupus nephritis; ESKD, end-stage kidney disease; MPA, mycophenolic acid; CYC, cyclophosphamide.

Table 2 Comparisons of parameters for children with lupus nephritis at start of MPA therapy and CYC therapy at 6 months, 12 months and 24 months.

	6 months			12 months			24 months		
	MPA group	CYC group		MPA group	CYC group		MPA group	CYC group	
	n = 15	n = 16	*p* value	n = 15	n = 15	*p* value	n = 14	n = 15	*p* value
Height (cm)	156.0 (153.0–164.0)	156.5 (147.0–160.0)	0.572	159.0 (154.0–164.0)	156.0 (147.0–160.0)	0.285	159.8 (155.5–165.0)	155.0 (147.0–160.0)	0.077
Body weight (kg)	53.4 (43.4–62.0)	52.5 (45.2–56.2)	0.682	55.9 (44.0–59.0)	53.1 (46.0–57.8)	0.567	52.5 (45.7–63.2)	52.0 (46.0–60.0)	0.591
BMI (kg/m^2)	19.4 (17.9–22.5)	21.6 (18.0–23.5)	0.682	20.9 (17.2–23.0)	21.2 (18.5–24.4)	0.567	20.2 (18.1–22.4)	21.3 (17.9–23.7)	0.561
WBC (K/uL)	6.6 (5.5–7.0)	7.9 (7.2–11.2)	0.024*	6.6 (5.4–7.2)	7.4 (5.0–9.1)	0.202	5.4 (4.2–7.6)	7.4 (5.4–8.8)	0.063
Hemoglobin (Hb, g/dL)	12.7 (11.6–13.2)	12.2 (10.8–13.2)	0.495	12.0 (11.5–13.1)	12.1 (11.2–12.7)	0.512	12.0 (11–14.2)	12.7 (10.5–13.1)	0.780
Platelet count (K/uL)	271.0 (244.0–345.0)	308.5 (240.3–340.5)	0.626	260.0 (231.0–323.0)	314.0 (249.0–348.0)	0.217	239.0 (189.3–309.0)	309 (244.0–338.0)	0.123
Serum creatinine (mg/dL)	0.6 (0.5–0.8)	0.8 (0.6–1.0)	0.078	0.7 (0.6–0.8)	0.8 (0.7–1.0)	0.089	0.7 (0.6–0.7)	0.7 (0.7–1.0)	0.158
Serum albumin (g/dL)	4.0 (3.5–4.2)	3.7 (3.0–3.9)	0.014*	4.0 (3.7–4.4)	4.2 (3.9–4.4)	0.461	4.1 (3.8–4.5)	4.2 (3.9–4.4)	0.847
GPT (U/L)	17.0 (13.0–22.0)	16.5 (12.3–22.3)	0.695	12.0 (8.3–20.3)	15.5 (10.5–19.3)	0.456	9.0 (7.3–10.8)	19.5 (14.0–29.8)	<0.001***
TG (mg/dL)	97.0 (65.5–225.5)	111.5 (81.3–154.5)	0.713	78.0 (70–104)	106.0 (87.0–134.0)	0.171	85.5 (74.3–122.8)	118.0 (78.8–160.0)	0.435
Anti-ds DNA (IU/ml)	37.5 (15–55.5)	22.4 (7.5–71.5)	0.709	40.0 (7.6–102.3)	15.1 (6.9–42.3)	0.270	38.0 (8.7–57.5)	13.5 (4.3–45.0)	0.605
C3 (mg/dL)	75.5 (61.1–87.5)	77.1 (67.8–107.3)	0.711	67.8 (57–84.7)	84.0 (71.2–94.3)	0.126	86.7 (49.6–101.3)	78.7 (69.4–92.0)	0.780
C4 (mg/dL)	14.7 (11.2–17.5)	16.1 (11.9–23.0)	0.338	11.8 (8.2–19.4)	17.3 (14.9–21.0)	0.041*	13.7 (8.1–19.3)	19.8 (13.4–21.3)	0.093
SLEDAI score	8.0 (6.0–8.0)	8.0 (3.0–10.0)	0.711	4.0 (2.0–10.0)	4.0 (2.0–8.0)	0.486	6.0 (2.0–10.5)	2.0 (0.0–8.0)	0.252
eGFR (mL/min/1.73 m^2)	99.4 (90.2–116.5)	82.3 (63.2–100.5)	0.030*	94.1 (85–120.6)	81.8 (65.3–93.3)	0.019*	97.8 (91.1–114.1)	84.2 (59.9–97.0)	0.046*

Continuous variables were presented by median (Q1-Q3) and Mann-Whitney U test. Significant level: $p < 0.05$*, $p < 0.01$**, $p < 0.001$***.

[a]In the MPA group, one patient was treated for less than 2 years, and the number of patients decreased to 14 at month 24 (n = 14).

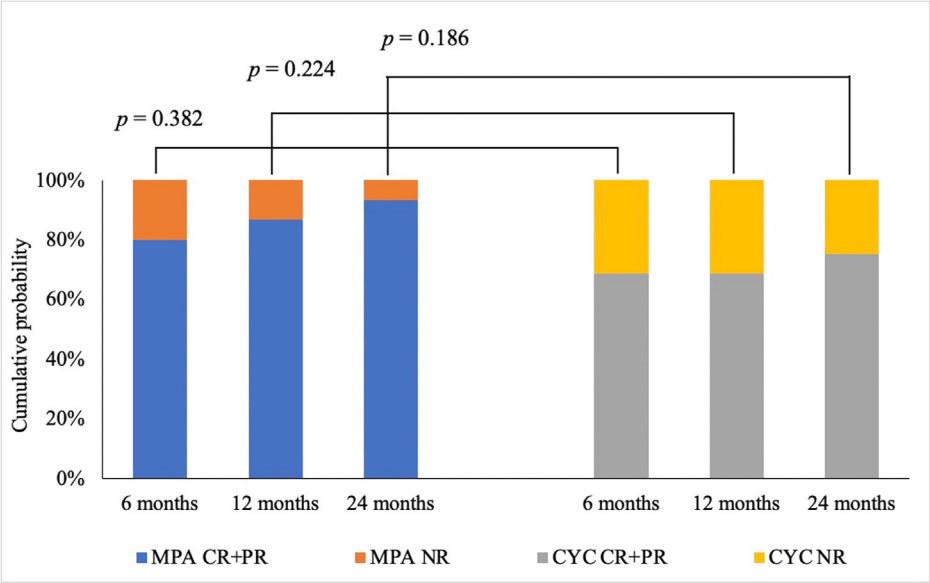
[b]In the CYC group, one patient developed ESKD after receiving induction therapy for 6 months. The data was excluded at month 12 and 24, and the patient numbers decreased to 15 in the CYC group at these timepoints (n = 15).

CYC, Cyclophosphamide; MPA, Mycophenolic acid; BMI, Body Mass Index; WBC, White blood cells count; GPT, Glutamic pyruvic transaminase; TG, Triglyceride; Anti-ds DNA, Anti-double stranded DNA antibody; C3, Complement factor 3; C4, Complement factor 4; SLEDAI, Systemic lupus erythematosus disease activity index; eGFR, estimated glomerular filtration rate; eGFR calculated using the New Schwartz formula.

Table 3 Comparisons of parameters for children with lupus nephritis at 6 months, 12 months and 24 months in two groups.

	MPA group				CYC group			
	Pre-induction	6 months	12 months	24 months	Pre-induction	6 months	12 months	24 months
	n = 15	n = 15	n = 15	n = 14	n = 16	n = 16	n = 15	n = 15
WBC (K/uL)	6.6 (4.3—9.8)	6.6 (5.5—7.0)	6.6 (5.4—7.2)	5.4 (4.2—7.6)	9.1 (4.5—14.7)	7.9 (7.2—11.2)	7.4 (5.0—9.1)	7.4 (5.4—8.8)
Hemoglobin (Hb, g/dL)	10.0 (8.5—10.6)	12.7 (11.6—13.2)**	12.0 (11.5—13.1)**	12.0 (11.0—14.2)*	10.3 (8.7—12.3)	12.2 (10.8—13.2)**	12.1 (11.2—12.7)	12.7 (10.5—13.1)
Platelet count (K/uL)	253.0 (209.0—271.0)	271.0 (244.0—345.0)*	260.0 (231.0—323.0)	239.0 (189.3—309.0)	211.5 (137.3—306.5)	308.5 (240.3—340.5)	314.0 (249.0—348.0)	309.0 (244.0—338.0)
Serum creatinine (mg/dL)	0.8 (0.6—1.1)	0.6 (0.5—0.8)	0.7 (0.6—0.8)	0.7 (0.6—0.7)	0.9 (0.8—1.7)	0.8 (0.6—1.0)*	0.8 (0.7—1.0)*	0.7 (0.7—1.0)*
Serum albumin (g/dL)	3.3 (2.7—3.7)	4.0 (3.5—4.2)**	4.0 (3.7—4.4)**	4.1 (3.8—4.5)**	2.8 (2.5—3.3)	3.7 (3.0—3.9)	4.2 (3.9—4.4)**	4.2 (3.9—4.4)**
GPT (U/L)	18.3 (9.5—32.0)	17.0 (13.0—22.0)	12.0 (8.3—20.3)*	9.0 (7.3—10.8)*	22.0 (12.4—36.3)	16.5 (12.3—22.3)	15.5 (10.5—19.3)	19.5 (14.0—29.8)
TG (mg/dL)	175.0 (94.5—266.0)	97.0 (65.5—225.5)	78.0 (70.0—104.0)*	85.5 (74.3—122.8)*	208.0 (142.5—296.5)	111.5 (81.3—154.5)*	106.0 (87.0—134.0)*	118.0 (78.8—160.0)*
Anti-ds DNA (IU/ml)	650.0 (48.3—2251.0)	37.5 (15.0—55.5)	40.0 (7.6—102.3)	38.0 (8.7—57.5)*	107.0 (25.0—1440.3)	22.4 (7.5—71.5)**	15.1 (6.9—42.3)**	13.5 (4.3—45.0)*
C3 (mg/dL)	44.7 (23.8—70.2)	75.5 (61.1—87.5)**	67.8 (57.0—84.7)**	86.7 (49.6—101.3)*	39.4 (27.2—56.8)	77.1 (67.8—107.3)**	84.0 (71.2—94.3)**	78.7 (69.4—92.0)**
C4 (mg/dL)	11.6 (5.3—13.9)	14.7 (11.2—17.5)	11.8 (8.2—19.4)	13.7 (8.1—19.3)	8.3 (3.5—11.7)	16.1 (11.9—23.0)**	17.3 (14.9—21.0)***	19.8 (13.4—21.3)***
SLEDAI score	14.0 (8.0—22.0)	8.0 (6.0—8.0)**	4.0 (2.0—10.0)**	6.0 (2.0—10.5)*	18.0 (16.0—20.0)	8.0 (3.0—10.0)***	4.0 (2.0—8.0)**	2.0 (0.0—8.0)**
eGFR (mL/min/1.73 m^2)	89.3 (59.1—105.1)	99.4 (90.2—116.5)*	94.1 (85.0—120.6)	97.8 (91.1—114.1)**	69.4 (39.7—77.6)	82.3 (63.2—100.5)*	81.8 (65.3—93.3)*	84.2 (59.9—97.0)*

Continuous variables were presented by median (Q1-Q3). Each time point was compared to the value of pre-induction by Wilcoxon Signed Rank test.
Significant level: $p < 0.05$*, $p < 0.01$**, $p < 0.001$***.
[a]In the MPA group, one patient was treated for less than 2 years, and the number of patients decreased to 14 at month 24 (n = 14).
[b]In the CYC group, one patient developed ESKD after receiving induction therapy for 6 months. The data was excluded at month 12 and 24, and the patient numbers decreased to 15 in the CYC group at these timepoints (n = 15).
CYC, Cyclophosphamide; MPA, Mycophenolic acid; WBC, White blood cells count; GPT, Glutamic pyruvic transaminase; TG, Triglyceride; Anti-ds DNA, Anti-double stranded DNA antibody; C3, Complement factor 3; C4, Complement factor 4; SLEDAI, Systemic lupus erythematosus disease activity index; eGFR, estimated glomerular filtration rate; eGFR calculated using the New Schwartz formula.



Fisher's exact test
MPA, mycophenolic acid; CYC, cyclophosphamide; CR, complete remission; PR, partial remission

Figure 2. Renal outcome after 6,12,24 months in both groups.

patients received MPA and 16 patients received CYC. Within the MPA group, 5 patients received MMF, and 10 patients received myfortic acid. The baseline demographic and laboratory data of these patients are shown in Table 1 and there were no significant differences between the two groups before induction therapy (month 0).

Following-up at months 6, 12, and 24

Table 2 presented a comparison of various parameters between MPA and CYC groups at months 6, 12, and 24. After induction therapy, eGFR was found to be significantly different between the MPA and CYC groups at month 6, 12 and 24 ($p < 0.05$). Additionally, WBC and ALB were statistically significant at month 6 between the two groups. At month 24, GPT was found to be significantly different between the MPA and CYC groups, and C4 was found to be significantly different at month 12. There was no significant difference in body height between the two groups.

In Table 3, we compared the laboratory parameters at follow-up periods (month 6, 12, and 24) versus pre-induction period (month 0) of each group. In the MPA group, Hb, serum ALB, C3 and SLEDAI score were statistically significant at months 6, 12, and 24 ($p < 0.05$). The eGFR improved significantly at months 6 and 24 ($p < 0.05$). PLT had significantly improved at month 6. GPT and TG showed a decreasing trend and were significantly different at months 12 and 24. Anti-dsDNA was significantly different at month 24. In the CYC group, serum creatinine level, eGFR, TG, anti-dsDNA, C3 and C4, and SLEDAI score were statistically significant at months 6, 12, and 24. Serum ALB was significantly improved at months 12 and 24, and Hb showed significantly improved at month 6 ($p < 0.05$).

Renal outcome at months 6, 12, and 24

Renal outcome is shown in Fig. 2. The primary endpoint was CR, and the secondary endpoint was PR. In the MPA group, CR occurred in 7/15 (47%) patients and PR in 5/15 (33%) patients at month 6. CR was achieved in 11/15 (73%) patients and PR in 2/15 (13%) at month 12; CR was seen in 11/15 (73%) patients and PR in 3/15 (20%) at month 24. In the CYC group, CR occurred in 5/16 (31%) patients and PR was reached in 6/16 (37.5%) patients at month 6. CR was achieved in 8/16 (50%) patients and PR in 3/16 (19%) patients at month 12; CR was seen in 9/16 (56%) patients and PR in 3/16 (19%) patients at month 24. NR occurred in 1/15 (7%) patients of the MPA group and in 4/16 (25%) patients of the CYC group at month 24. Response rate of complete and partial remission (CR + PR) was achieved in 80% of the MPA group and 69% of the CYC group at month 6, 87% in the MPA group and 69% in the CYC group at month 12, and 93% in the MPA group and 75% in the CYC group at month 24. The cumulative probability of CR and PR was not statistically different between the two groups at month 6 ($P = 0.382$), month 12 ($P = 0.224$), and month 24 ($P = 0.186$).

Discussion

The aim of this study was to compare the efficacy of MPA and CYC as treatment for pLN. Tables 2 and 3 showed the comparison of various parameters between MPA and CYC as pLN therapy. It is highlighted that serum ALB in the MPA group was within the normal range and its improvement had reached statistical significance at month 6, while that in the CYC group was also within the normal range but its improvement had no statistical significance at month 6. At month 6, eGFR in both groups had reached statistical

significance at month 6, however only the one in the MPA group was within the normal range. As regards to SLE disease activities, while C3 levels improved in each group, C4 levels showed significantly improved in the CYC group at month 6, 12 and 24 ($p < 0.05$). This finding can be used as a reference for observing the clinical condition of pLN patients.

Although many observational and randomized trials have reported on the efficacy of therapies for LN, the relationships between the data and the age of the cohorts should be noted. A retrospective cohort study by Tian et al. found that by the fourth year of MMF therapy for childhood-onset proliferative LN, there was a significant improvement in the eGFR, and remission was maintained until the end of the study.[24] The results of this study were corrected for potential confounding by indication, and the large cohort finding was consistent with trial evidence for adult proliferative LN.

Previous studies suggested that MPA could be an effective alternative to CYC for treating adult LN, and that this could be also true for pLN.[14,15] A meta-analysis by Jiang et al. found that MMF was better than CYC as induction treatment at promoting complete remission in LN patients aged 15—48. CYC may be superior to MMF in Asian patients or those with initial urine protein levels that were lower than 4 g/day when used to reduce urine protein. These data were collected from adolescents and adults, and we could benefit from this study.[14] Anutrakulchai et al. also reported that myfortic acid could be used as an alternative treatment for relapsed or resistant proliferative LN in Asian patients. Myfortic acid may have comparable efficacy and was better tolerated than CYC.[15] A recent cohort study by Smith et al. compared MMF and CYC as induction therapies in patients with proliferated juvenile-onset LN and found that they were comparably efficacious in terms of treatment response, damage accrual, and time to next flare.[25] This large cohort study could also support the results of our study.

Considering the adverse effects of CYC such as infertility, the dose of CYC may require adjustment in the future.[11] Although our study did not track long-term gonadal damage of patients who received CYC for pLN, other studies had compared the therapeutic effect of high-dose and low-dose CYC to provide recommendations for the clinical use.[26,27] Houssiau et al. conducted a prospective study, the Euro-Lupus Nephritis Trial (ELNT), designed to compare high-dose IV CYC (not following the NIH protocol) and low-dose IV CYC as remission-inducing therapy for proliferative LN.[26] In both treatment groups, azathioprine was used as long-term immunosuppressive therapy. The result showed that renal remission was achieved in 71% of the low-dose group and in 54% of the high-dose group (not statistically significant). A web-based survey by Cannon et al. revealed that 32% of pediatric nephrologists chose EuroLupus dosing for cSLE in 2020, compared to 6% of the same group in 2009. The provider factors associated with choosing the low-dose CYC included familiarity with the protocol (OR 4.2, $P = 0.006$).[27] More importantly, it is likely that low-dose CYC will be the preferred pLN remission-inducing treatment in the future, due to concerns of the toxicity of CYC. MPA did not have association with an increased risk of hemorrhagic cystitis or gonadal toxicity during treating LN.[28] MPA becomes an optional therapy for pLN when considering the desire to maintain gonadal function.

The other issue was the preference of induction therapy for pLN. While the selection of MPA or CYC for LN induction treatment was based on individual physician's preference, neither MMF nor myfortic acid is paid for by the NHI in Taiwan. Therefore, determining the use of MPA would depend on the economic status of the family. On the other hand, CYC was cost-effective with intravenous use, better compliance and was paid by the NHI for LN treatment.[29] The prices of the two drugs could be a potential bias in the study.

The main limitation of our study was that this was a single center study, with a retrospective design, and a small sample size. In the future, a multicenter study is desirable for comparing the response of MPA and CYC as a pLN treatment in Taiwan.

In conclusion, the significant improvement in the eGFR was superior in the MPA group at months 6, 12 and 24 compared to that in the CYC group. Although renal response showed no statistically significant differences between the two groups, the study demonstrated the comparability of the two drugs. MPA and CYC can be used for improving pLN disease condition, and the efficacy of MPA is non-inferior to that of CYC for pLN treatment. However, more studies are required to clarify the efficacy, relative safety, and adverse effects of MPA and CYC for pLN treatment in Taiwan.

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Declaration of competing interest

The authors had no competing interests.

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