ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Mycophenolate mofetil versus cyclophosphamide, in combination with prednisolone for lupus nephritis induction treatment: Findings from a prospective observational study

Rakhesh LR[1], Priya S Raju[2], Rajesh Wilson[3], Bindu Latha Nair R[4], Sanitha Kuriachan[5], Mahesh Kumar D[6], Jumi Jacob[7]

[1]Associate Professor, Department of Pharmacology, [2]Associate Professor, Department of Obstetrics and Gynecology, Dr. Moopen's Medical College, Wayanad, [3]Assistant Professor, Department of Biochemistry, Karuna Medical College, Palakkad, [4]Professor, Department of Pharmacology, Government Medical College, Thiruvananthapuram, [5]Professor, Department of Pharmacology, Jubilee Mission Medical College and Research Institute, Thrissur, [6]Associate Professor, Department of Pharmacology, Amrita Institute of Medical Sciences, Kochi, [7]Associate Professor, Department of Pharmacology, Sree Uthradom Thirunal Academy of Medical Sciences, Vencode, Vattappara, Thiruvananthapuram, Kerala, India

Submission: 28-04-2025 Revision: 04-06-2025 Publication: 01-07-2025

ABSTRACT

Background: Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus. Intravenous cyclophosphamide (CYC) is the standard induction therapy for proliferative LN, but it is associated with serious adverse effects such as sterility and bone marrow suppression. Mycophenolate mofetil (MMF) has emerged as a promising alternative, offering better renal outcomes and preserving fertility in women of childbearing age. **Aims and Objectives:** To compare the treatment outcomes and safety of MMF plus prednisolone versus CYC plus prednisolone in the induction treatment of LN. **Materials and Methods:** Patients with Class 3 and 4 LN who received either oral MMF (2 g/day) or CYC (0.75–1 g/m^2) were included in the study. Remission rates and adverse events were measured as treatment outcomes. **Results:** The study found 81% remission in the MMF group compared to 76.4% in the CYC group (not statistically significant). Adverse effects in the MMF group included headache (52.4%), bone marrow toxicity (47.6%), back pain (42.9%), and gastrointestinal side effects (42.8%). The CYC group had higher rates of bone marrow toxicity (57.1%), respiratory infections (33.3%), and mucocutaneous infections (57.1%). Notably, alopecia (4.8% vs. 52.4%, P = 0.001) and amenorrhea (4.8% vs. 28.6%, P = 0.04) were significantly lower in the MMF group. **Conclusion:** The MMF-steroid regimen is highly effective for inducing remission in proliferative LN and offers a more favorable safety profile than the CYC-steroid regimen.

Key words: Lupus nephritis; Mycophenolate mofetil; Remission induction; Cyclophosphamide; Side effects

Access this article online

Website: https://ajmsjournal.info/index.php/AJMS/index

DOI: 10.71152/ajms.v16i7.4589

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the production of autoantibodies and immune complexes that can affect virtually any organ system. Among the various manifestations of SLE, lupus nephritis (LN) is one of the most severe complications, leading to significant morbidity

Address for Correspondence:
Jumi Jacob, Associate Professor, Department of Pharmacology, Sree Uthradom Thirunal Academy of Medical Sciences, Vencode, Vattappara – 695028, Thiruvananthapuram, Kerala, India. **Mobile:** +91-9400521826. **E-mail:** jumijacob@gmail.com

and mortality. LN occurs in approximately 50% of SLE patients and is a major predictor of poor prognosis due to its potential to progress to end-stage renal disease if not adequately treated.

The treatment of LN typically involves a two-phase approach: an induction phase aimed at achieving rapid disease control and remission, followed by a maintenance phase to prevent relapse and sustain remission. Historically, intravenous (IV) cyclophosphamide (CYC) has been the cornerstone of induction therapy for proliferative LN (Class III and IV), as classified by the International Society of Nephrology/Renal Pathology Society (ISN/RPS). However, CYC is associated with considerable toxicity, including risks of infertility, infections, and malignancies, which necessitate the exploration of alternative therapies.

Mycophenolate mofetil (MMF) is a promising alternative to CYC for the induction treatment of proliferative LN. MMF is an immunosuppressive agent that inhibits inosine monophosphate dehydrogenase, crucial for the proliferation of T and B lymphocytes. Recent studies have suggested that MMF may offer comparable, if not superior, efficacy to CYC in inducing remission of LN, with a more favourable safety profile, particularly in terms of preserving fertility and reducing the risk of severe adverse effects.[1-4] Tselios et al. analyzed the impact of different initial prednisone doses in combination with MMF and CYC, finding that medium doses of prednisone were effective in inducing remission when used with MMF, thus potentially reducing the time to remission and the burden of steroid-related side effects.[5]

Given the significant impact of LN on patient quality of life and the potential for serious side effects, it is essential to continually evaluate and compare the treatment outcomes and safety of available treatment options. With this background, this study aims to assess the treatment outcome of MMF plus prednisolone in the induction treatment of LN, compared to the standard regimen of CYC plus prednisolone.

Aims and objectives

To compare the treatment outcomes and safety of MMF plus prednisolone versus CYC plus prednisolone in the induction treatment of LN.

MATERIALS AND METHODS

This was a prospective observational study conducted in the Department of Nephrology in a tertiary care teaching hospital over 12 months. The study population was comprised patients diagnosed with Class 3 or Class 4 LN based on the ISN/RPS classification, confirmed by renal biopsy, who received oral MMF plus prednisolone or IV CYC plus prednisolone.

Inclusion criteria were patients aged 18–65 years of either sex, with biopsy-proven Class 3 or 4 LN, who provided written informed consent. Exclusion criteria included patients with significant comorbidities such as diabetes mellitus, coronary artery disease, stroke, or other autoimmune conditions; pregnant or lactating women; those with serum creatinine (SCr) ≥4 mg/dL; and critically ill patients.

All eligible patients attending the nephrology outpatient department who met the inclusion criteria were enrolled using purposive sampling. After obtaining informed written consent, data were collected using a structured pro forma that included demographic details, clinical examination findings, and relevant laboratory parameters extracted from the case records.

The sample size was calculated based on the primary objective of assessing the effectiveness of MMF plus prednisolone in inducing remission. Assuming a remission rate of 83% based on prior literature,[6] With a 20% margin of error, the minimum required sample size was calculated to be 21. An equal number of patients receiving IV CYC plus prednisolone were enrolled for comparison.

The study was conducted after obtaining clearance from the institutional ethics committee (via Letter No. IEC No. 07/26/2016/MCT dated December 29, 2016). Written informed consent was obtained from all participants before their inclusion. Study tools included the informed consent form and a structured pro forma.

Patients in the MMF group received oral MMF at a dose of 2 g/day, along with corticosteroids. Steroid therapy included IV methylprednisolone 500 mg daily for 3 days, followed by oral prednisolone at 1 mg/kg/day for 6 weeks, tapered weekly over the next 18 weeks to a maintenance dose of 10 mg/day by 6 months. Patients in the CYC group received IV CYC at a dose of 0.75–1 g/m^2 along with the same steroid regimen.

Each patient was evaluated at 4 time points: Baseline (initial visit) and 6 months after initiating therapy. During each visit, clinical and laboratory data were recorded and entered into the structured pro forma.

The effectiveness was assessed by evaluating the remission status at 6 months, defined as either complete or partial remission. Complete remission was defined as a return of SCr to baseline levels along with a urine protein-to-

creatinine ratio (uPCR) <500 mg/g (<50 mg/mmoL). Partial remission was defined as a stabilization (±25%) or improvement in SCr without normalization, along with a ≥50% reduction in uPCR. Safety was evaluated by identifying adverse drug reactions during the induction phase based on patient interviews, clinical examination, and laboratory investigations.

Data entry was performed using Microsoft Excel, and analysis was carried out using SPSS version 16. Categorical variables were described as percentages, and continuous variables were summarized using mean, standard deviation, minimum, and maximum values. Comparisons between groups for categorical variables were conducted using Pearson's Chi-square test, and independent sample t-test and paired T-test were used for continuous variables. A P<0.05 was considered statistically significant.

RESULTS

This prospective observational study was conducted in the Department of Nephrology, Government Medical College, Thiruvananthapuram, from June 2017 to May 2018. A total of 42 patients with biopsy-proven Class 3 or 4 LN were included. Of these, 21 patients were treated with oral MMF plus prednisolone, and an equal number received IV CYC plus prednisolone to serve as a comparison group for the secondary objective. Patients were evaluated at baseline and followed up at the end of 6th month of induction therapy.

Baseline demographic and clinical characteristics

The mean age of patients in the MMF plus prednisolone group was 26.19±6.56 years, whereas it was 27.86±4.63 years in the CYC group, with a majority of patients in both groups being under the age of 30 (76.2% vs. 71.4%). The vast majority were female (95.2% in the MMF group vs. 90.5% in the CYC group). Regarding disease severity, 38.1% of MMF group patients had Class 3 LN, compared to 42.9% in the CYC group. Meanwhile, 61.9% and 57.1% of patients in the MMF and CYC groups, respectively, had Class 4 disease, indicating comparable baseline characteristics between the groups (Table 1).

The treatment outcome of the MMF-steroid regimen and the CYC-steroid regimen (n = 42)

The treatment outcome of the oral MMF plus prednisolone regimen was evaluated in 21 patients with Class 3 or 4 LN. Treatment outcome was measured as either complete or partial remission within 6 months of induction therapy. Complete remission was defined as a return of SCr to baseline and a reduction of uPCR to <0.500 mg/g, while partial remission was defined as stabilization or improvement in SCr with a ≥50% reduction in uPCR.

Among patients in the MMF group, 17 out of 21 (81%) achieved remission, with 4 patients (19%) classified as treatment failures. The remission rate was thus high, and the regimen was found to be effective for induction treatment in proliferative LN. The mean SCr decreased significantly from 2.319±1.078 mg/dL at baseline to 1.559±1.211 mg/dL at 6 months (P<0.001). Similarly, the mean uPCR significantly declined from 1010±279 to 494±257 mg/g (P<0.001), indicating a robust renal response to treatment. In addition, anti-dsDNA levels, a serologic marker of disease activity, showed a significant reduction from 383±183.9 IU/mL to 152.1±156.9 IU/mL (P<0.001), supporting both clinical and immunological response to therapy.

In the CYC group, 16 out of 21 patients (76.2%) achieved remission, and 5 patients (23.8%) were classified as failures. Although the remission rate was slightly lower than that observed with MMF, the difference between the two groups was not statistically significant (P=0.707, Chi-square test) (Table 2).

Safety profile and comparative analysis

The MMF group showed higher rates of headache (52.4%), bone marrow suppression (47.6%), GI side effects (42.8%), and back pain (42.9%). Mucocutaneous infections, dysuria, and fever occurred in 28.6%, 19%, and 19%, respectively, while amenorrhea and alopecia were each reported in 4.8%.

Compared to MMF, the CYC group had higher – but not statistically significant – rates of bone marrow toxicity (57.1%, P=0.537) and mucocutaneous infections (57.1%, P=0.061). Amenorrhea (28.6% vs. 4.8%, P=0.038) and alopecia (52.4% vs. 4.8%, P=0.001) were significantly more frequent with CYC. GI symptoms were more common with MMF, especially diarrhea (23.8% vs. 4.8%, P=0.078). Subtypes of bone marrow suppression varied between groups but showed no significant differences (Table 3).

DISCUSSION

This prospective observational study compared the treatment outcomes of MMF plus prednisolone versus IV CYC plus prednisolone as induction therapy for Class III and IV LN. The findings support MMF as a non-inferior and potentially safer alternative to CYC, especially in populations where fertility preservation and tolerability are priorities.

In the present study, 81% of patients receiving MMF achieved remission compared to 76.2% in the CYC group. Although the difference was not statistically significant (P=0.707), the trend toward better outcomes with MMF aligns with findings from Ginzler et al., who reported

Table 1: Baseline demographic and clinical characteristics of patients on MMF-prednisolone regimen and cyclophosphamide-steroid regimen (n=42)

Characteristics	Category	MMF n=21 (%)	Cyclophosphamide n=21(%)
Age	<30 years	16 (76.2)	15 (71.4)
	≥30 years	5 (23.8)	6 (28.6)
Gender	Male	1 (4.8)	2 (9.5)
	Female	20 (95.2)	19 (90.5)
LN classification	Class 3	8 (38.1)	9 (42.9)
	Class 4	13 (61.9)	12 (57.1)

MMF: Mycophenolate mofetil, LN: Lupus nephritis

Table 2: Treatment outcome of MMF-steroid regimen and cyclophosphamide-steroid regimen (n=42)

Parameter	MMF+Steroid	CYC+Steroid	P-value
Remission (n, %)	17 (81)	16 (76.2)	1
Failure (n, %)	4 (19)	5 (23.8)	0.707
Serum creatinine (mg/dL)-Baseline	2.32±1.08	2.41±1.06	0.242
Serum creatinine (mg/dL)-6 months	1.56±1.21	1.68±1.19	0.703
Urine PCR (mg/g)-Baseline	1.01±0.28	1.05±0.31	0.182
Urine PCR (mg/g)-6 months	0.49±0.26	0.52±0.27	0.476
Anti-dsDNA (IU/mL)-Baseline	383.0±183.9	390.2±171.4	0.977
Anti-dsDNA (IU/mL)-6 months	152.1±156.9	165.3±149.7	0.476

MMF: Mycophenolate mofetil, PCR: Protein creatinine ratio, CYC: Cyclophosphamide

significantly higher complete remission rates with MMF compared to IV CYC (22.5% vs. 5.8%, P=0.005) in a 24-week multicenter trial.[7] Similarly, Rathi et al. found that MMF and low-dose CYC had comparable response rates in Indian patients with proliferative LN (54% vs. 50%), supporting MMF as an effective alternative in real-world clinical settings.[8]

Further support comes from Li et al., who evaluated a multitarget regimen (MMF, tacrolimus, and steroids) and observed higher response rates (83.5%) compared to IV CYC (63.0%) and a shorter time to remission.[9] Although our study did not employ a multitarget approach, the overall benefit of MMF in this cohort remains consistent with global data.

Renal function and serologic activity improved significantly in both groups. Mean SCr and uPCR decreased in parallel

Table 3: Safety profile and comparative analysis of adverse drug reactions between MMF plus steroid and cyclophosphamide plus steroid regimens

Adverse effect	MMF (n, %)	CYC (n, %)	P-value
Bone marrow toxicity	10 (47.6)	12 (57.1)	0.537
Thrombocytopenia	6 (28.6)	3 (14.3)	0.259
Anemia	3 (14.3)	5 (23.8)	0.432
Leukopenia	1 (4.8)	4 (19.0)	0.153
Mucocutaneous infections	6 (28.6)	12 (57.1)	0.061
Bacterial infection	3 (14.3)	4 (19.0)	0.679
Fungal infection	3 (14.3)	8 (38.1)	0.079
Herpes infection	0 (0.0)	1 (4.8)	0.311
Amenorrhea	1 (4.8)	6 (28.6)	0.038
Alopecia	1 (4.8)	11 (52.4)	0.001
GI side effects (overall)	9 (42.8)	7 (33.3)	0.525
Nausea	4 (19.0)	4 (19.0)	1
Vomiting	2 (9.5)	1 (4.8)	0.549
Diarrhea	5 (23.8)	1 (4.8)	0.078
Abdominal pain	2 (9.5)	2 (9.5)	1
Headache	11 (52.4)	9 (42.9)	0.537
Skin lesions	0 (0.0)	2 (9.5)	0.147
Dysuria	4 (19.0)	7 (33.3)	0.292
Edema	6 (28.6)	8 (38.1)	0.513
Fever	4 (19.0)	6 (28.6)	0.469
Back pain	9 (42.9)	9 (42.9)	1

MMF: Mycophenolate mofetil, CYC: Cyclophosphamide, GI: Gastrointestinal

with reductions in anti-dsDNA titers, indicating favorable responses. This is consistent with outcomes from Chan et al., (2005), who showed that both MMF and CYC achieved similar improvements in renal parameters with fewer adverse events in the MMF group.

Safety analysis highlighted important differences. Gastrointestinal (GI) symptoms were more common in MMF-treated patients (42.8%) compared to CYC (33.3%), with diarrhea being most prevalent. This is consistent with reports from Ginzler et al., (2005), where GI side effects were more frequent with MMF but generally manageable.

Adverse effects affecting reproductive health and appearance were significantly more frequent in the CYC group, with alopecia reported in 52.4% and amenorrhea in 28.6% of patients compared to just 4.8% in the MMF group for both. These findings align with prior studies such as Contreras et al., (2004), which documented CYC-induced gonadal toxicity and hair loss as limiting factors in long-term adherence.

Infections, particularly mucocutaneous types, were more frequent in the CYC group (57.1% vs. 28.6%), nearly reaching statistical significance (P=0.061). This observation is supported by Faroque et al., (2016), who found a higher frequency of infection-related hospitalizations in patients on CYC-based regimens in a large South Asian cohort.

Taken together, these results suggest that MMF is a viable and often preferable first-line induction agent in proliferative LN. Particularly in women of reproductive age, MMF offers the advantage of efficacy with fewer long-term risks. However, patient selection and monitoring remain critical, and CYC may still be suitable in severe or refractory cases, especially in resource-constrained settings.

Clinical implications

Our findings align with growing global and regional evidence advocating for MMF as a first-line induction agent in LN, particularly among young women where fertility preservation is essential. CYC may still be preferred in resource-limited settings or patients with severe or rapidly progressive disease due to cost-effectiveness and familiarity.

Moreover, newer protocols-such as the multitarget regimen including tacrolimus-have shown even better outcomes than MMF alone, offering potential avenues for improved induction therapy, particularly in Asian cohorts.

Limitations of the study

The study is limited by its small sample size, single-center design, and short duration. A longer follow-up would help assess renal flare rates, progression to chronic kidney disease, and long-term adverse events.

CONCLUSION

This study reaffirms the comparable efficacy of MMF and CYC in inducing remission in Class III and IV LN. However, MMF demonstrates a superior safety profile, especially concerning reproductive and GI adverse effects. Given its tolerability and efficacy, MMF plus prednisolone may be considered the preferred induction therapy in eligible patients, aligning with current recommendations and evidence-based practice.

ACKNOWLEDGMENT

We are grateful to the faculty and staff of the Department of Pharmacology and the Department of Nephrology at Government Medical College, Thiruvananthapuram, for their valuable input and encouragement.

REFERENCES

1. Choi SE, Park DJ, Kang JH, Lee KE, Xu H, Lee JS, et al. Comparison of renal responses to cyclophosphamide and mycophenolate mofetil used as induction therapies in Korean patients with lupus nephritis. J Rheum Dis. 2019;26(1):57-65. https://doi.org/10.4078/jrd.2019.26.1.57
2. An Y, Zhou Y, Bi L, Liu B, Wang H, Lin J, et al. Combined immunosuppressive treatment (CIST) in lupus nephritis: A multicenter, randomized controlled study. Clin Rheumatol. 2019;38(4):1047-1054. https://doi.org/10.1007/s10067-018-4368-8
3. Anders HJ and Hiepe F. Treatment options for refractory lupus nephritis. Clin J Am Soc Nephrol. 2019;14(5):653-655. https://doi.org/10.2215/CJN.03230319
4. Gul H, Mushtaq MS, Salim B, Samreen S, Nasim A and Khan M. A comparison of mycophenolate mofetil and cyclophosphamide as lupus nephritis induction therapy. J Ayub Med Coll Abbottabad. 2020;32(4):454-458.
5. Tselios K, Gladman DD, Al-Sheikh H, Su J and Urowitz MB. Medium versus high initial prednisone dose for remission induction in lupus nephritis: A propensity score-matched analysis. Arthritis Care Res (Hoboken). 2022;74(9):1451-1458. https://doi.org/10.1002/acr.24592
6. Cross J, Dwomoa A, Andrews P, Burns A, Gordon C, Main J, et al. Mycophenolate mofetil for remission induction in severe lupus nephritis. Nephron Clin Pract. 2005;100(3):c92-c100. https://doi.org/10.1159/000085054
7. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2025;353(21):2219-2228. https://doi.org/10.1056/NEJMoa043731
8. Rathi M, Goyal A, Jaryal A, Sharma A, Gupta PK, Ramachandran R, et al. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. Kidney Int. 2016;89(1):235-242. https://doi.org/10.1038/ki.2015.318
9. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2015;16(6):619-629. https://doi.org/10.1016/S1470-2045(15)70156-7

Authors Contribution:
RLR, BLNR, PSR- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation, and submission of the article; **JJ**- Concept, design, clinical protocol, manuscript preparation, editing, coordination, and manuscript revision; **SK, MKD**- Design of study, statistical analysis and interpretation, review manuscript, literature survey, and preparation of figures.

Work attributed to:
Government Medical College, Thiruvananthapuram, Kerala, India.

Orcid ID:
Rakhesh LR - https://orcid.org/0009-0000-4809-3910
Priya S Raju - https://orcid.org/0009-0008-8964-0341
Rajesh Wilson - https://orcid.org/0000-0003-0558-6883
Sanitha Kuriachan - https://orcid.org/0000-0002-2711-9816
Mahesh Kumar D - https://orcid.org/0000-0002-0535-601X
Jumi Jacob - https://orcid.org/0009-0002-0763-1975

Source of Support: Nil, **Conflicts of Interest:** None declared.