https://doi.org/10.29309/TPMJ/2025.32.10.9834

The Professional Medical Journal
www.theprofesional.com
2025, Volume, 32 Issue, 10

ORIGINAL ARTICLE

Mycophenolate mofetil versus cyclophosphamide as induction therapy in lupus nephritis at one year- a prospective cohort study.

Maimoona Firdus[1], Rashid Usman[2], Maryam Ahmed[3], Saira Yasmin[4], Shahida Parveen[5], Babur Salim[6]

Article Citation: Firdus M, Usman R, Ahmed M, Yasim S, Parveen S, Salim B. Mycophenolate mofetil versus cyclophosphamide as induction therapy in lupus nephritis at one year- a prospective cohort study. Professional Med J 2025; 32(10):1288-1293. https://doi.org/10.29309/TPMJ/2025.32.10.9834

ABSTRACT… Objective: To compare efficacy of mycophenolate mofetil to intravenous cyclophosphamide as inductive therapy for lupus nephritis at 1 years after induction. **Study Design:** Observational Prospective Cohort study. **Setting:** Department of Rheumatology, Fauji Foundation Hospital Rawalpindi, Pakistan, **Period:** 26th Jan, 2024 to 28th Feb 2025. **Methods:** Sixty two LN patients of both genders and at least 18 years of age were recruited into MMF & CYC groups with equal numbers in each group. Induction therapy with MMF & IV CYC were given for 6 months in the respective group followed by MMF for next 6 months. CRR, PRR and TRR were obtained at 1 year after induction. Excel software was used to analyse the data obtained. **Results:** The mean age of the patients in MMF group was 39.68±5 years while the mean age of the patients in CYC group was 37.45±4.87 years. Female gender outnumbered in both the groups. At 1 year of induction therapy, complete renal remission (CRR) in MMF group was observed in 77% patients while in CYC group it was observed in 29% patients. Partial renal remission (PRR) in MMF group was observed in 16% patients while in CYC group it was observed in 16% patients. Total renal remission (TRR) in MMF group was observed in 94% patients while in CYC group it was observed in 45% patients. **Conclusion:** MMF is more affective as induction therapy for lupus nephritis as compared to IV CYC. Moreover it is more safe and tolerable.

Key words: Cyclophosphamide, Induction Therapy, Lupus Nephritis, Mycophenolate Mofetil.

INTRODUCTION

Kidneys are most commonly affected in patients with systemic lupus erythematosus (SLE) as a result of damage to glomeruli, tubule-interstitial tissues, and blood vessels. Lupus nephritis (LN) occurs in about 40% of all patients with SLE, and usually within the first five years following diagnosis. Nevertheless, in spite of more advanced treatment, LN is still considered as a serious risk factor for development of renal failure, having a progression rate of 4.3% to 10.1%. Failing kidneys, along with infections, malignancies, and cardiovascular injuries lead to death in SLE patients. The risk of developing LN also varies considerably among different ethnic groups, and the clinical features can vary substantially-from almost asymptomatic urinary abnormalities to severe cases manifesting as nephritic syndrome or an almost rapid decline in kidney functions.[1]

The last four decades have been very fruitful in terms of novel therapeutic modalities for lupus nephritis (LN), administering corticosteroids at very high doses, intravenous cyclophosphamide (CYC), and mycophenolate mofetil (MMF), which has greatly improved clinical outcomes.[2] Current treatment guidelines have recognized both MMF and CYC as standard first-line induction therapies for LN, largely due to RCTs that have proven equivalent effectiveness of both in terms of gut function and renal economy. These are meant to be more tolerable in efficacy as MMF is safer than CYC, which is linked with a higher number of adverse effects. However, both remain the two cornerstones and primary agents of management for LN, and this fact underlines the valuable place that modern treatment protocols occupy.[3-5]

1. FCPS (Medicine), Resident Rheumatology, FFH, Rawalpindi.
2. FCPS (Neurology), Consultant Neurologist, Prime Teaching Hospital, Peshawar.
3. FCPS (Medicine), Resident Rheumatology, FFH, Rawalpindi.
4. FCPS (Medicine), Resident Rheumatology, FFH, Rawalpindi.
5. FCPS (Medicine), FCPS (Rheumatology), Consultant Rheumatologist, FFH, Rawalpindi.
6. FCPS (Medicine), FCPS (Rheumatology), Consultant Rheumatologist, FFH Rawalpindi.

Correspondence Address:
Dr. Maimoona Firdus
Department of Rheumatology
FFH, Rawalpindi.
maimoonamarwat313@gmail.com

Article received on: 06/03/2025
Accepted for publication: 19/05/2025

Therapy to induce rapid remission is of utmost importance to safeguard renal function and long-term outcome.[6] Intravenous cyclophosphamide has been the standard induction agents supported by the NIH trials. However, it has a limited application due to its toxicity, which includes gonadal toxicity and opportunistic infections. As a promising alternative, mycophenolate mofetil has shown, via the Aspreva Lupus Management Study (ALMS), to be non-inferior to IVC in attaining renal response at 24 weeks, with a more favourable safety profile.[7]

But there still remains a question about the long-term effectiveness, particularly after a year follows induction. Long-term effectivity when compared between the MMF and IVC, although real-world data show variations according to the existing influencing factors such as adherence, comorbidities, and other demographics.[8] Considerable recent advances, including the use of biologics like rituximab, have made treatment situations even more complicated, necessitating fresh comparisons between the older agents.[9]

Existing studies mostly target short-term outcomes, leaving evidence gaps concerning sustained renal response and safety beyond one year. Research on the management of LN has not been duly addressed in Pakistan. The subject lacks local data as most studies have been done in Caucasian, African American, and Chinese populations. This study, therefore, will compare the efficacy of MMF with IV CYC in LN as induction therapy at a year with the renal response rates assessed.

METHODS

This observational prospective cohort study was conducted at department of Rheumatology, Fauji Foundation Hospital Rawalpindi, Pakistan, from 26th Jan, 2024 to 28th Feb 2025. Ethical approval was obtained from Ethical Review Committee, Fauji Foundation Hospital Rawalpindi, Pakistan under reference No. 933/RC/FFH/RWP. Sample size was 62 patient, 31 patients in each group determined through OpenEpi sample size calculator by taking complete renal response in mycophenolate mofetil group to be 71.4%[10] & complete renal response in intravenous cyclophosphamide group to be 36.4%[10], power of test 80% & significance level of 95%. All LN patients of both genders and at least 18 years of age, visiting the rheumatology unit were included in the study after verbal invitation and briefing them about the details of the study and data collection. Diagnosis of LN was defined as persistent proteinuria ≥0.5gm/24 hours or UPCR ≥0.5gm/gm with or without active urinary sediment in at least two urine samples within 6 weeks.[11] Patients were divided into two groups i.e., mycophenolate mofetil (MMF) group & intravenous cyclophosphamide (IV CYC) group, with equal number of participant in each. Patients age, gender, pretreatment total urinary 24 hours urinary protein, pretreatment serum creatinine and any pretreatment hematuria were noted in both groups. All the participants were followed till 1 year of the initiation of the treatment. Patients with inconsistent follow-ups or who were non-compliant with their medications were excluded. The IV CYC group received intravenous cyclophosphamide (CYC) as per the Euro Lupus Nephritis Trial protocol comprising i.e., 500mg intravenous cyclophosphamide (CYC) every two weeks for three months and the MMF group received oral mycophenolate mofetil (MMF) 2-3 gm/day as tolerated for six months as induction therapy. Both the groups also received intravenous methylprednisolone 3gm at the start, followed by oral prednisolone 0.5mg/kg/day for 30 days and tapering to 10mg/day over the next 2 months. Both the groups also received oral hydroxychloroquine, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) if not contraindicated. All patients in the MMF group continued it beyond six months of induction as maintenance. Patients in the IV CYC group were transitioned to MMF after six months of induction. The maintenance dose of MMF was gradually increased to a maximum of 2 grams per day. Additionally, tacrolimus (TAC) was introduced at a dose of 0.05 mg/kg/day alongside MMF, if a patient experienced disease flare. In case of intolerance to MMF, it was replaced with TAC.

At 1 year of treatment total urinary 24 hour's urinary

protein, serum creatinine, hematuria were again noted in both groups. Complete renal remission (CRR) and partial renal remission (PRR) were assessed 1 year after starting induction therapy. CRR was defined as a 24-hour urine total protein (24h-UTP) of less than 0.5 g, with serum creatinine (SCr) remaining within 10% of the baseline value. PRR was defined as at least a 50% reduction in 24h-UTP to a level below the nephrotic range but still above 0.5 g, with SCr also staying within 10% of baseline. The total renal remission (TRR) was the combined total of both CRR and PRR.

Excel software was used to analyze the data obtained. Categorical variable were described as percentages and continuous variables were described as mean± standard deviations. Student t test and chi square test both at p value <5% significance were applied where needed.

RESULTS

The mean age of the patients in MMF group was 39.68±5 years while the mean age of the patients in CYC group was 37.45±4.87 years with p value of 0.0276. Female gender outnumbered in both the groups. Pre induction 24 hours urinary protein was 3.65±1.08 g/dl in MMF group while 3.65±0.36 g/dl in CYC group with p value of 0.4938. Pre induction serum creatinine in MMF group was 74.88±7.55 mmol/L while in CYC group was 78.98±9.29 with p value of 0.000029.

Pre induction hematuria in MMF group was in 17 (55%) patients and in CYC group it was in 16 (52%) patients with p value of 0.7990. Pre induction C3 level was in MMF group was 0.48±0.09 while in CYC group was 0.48±0.09 with p value of 0.4188. Pre induction C4 level was in MMF group was 0.13±0.17 while in CYC group was 0.11±0.06 with p value of 0.2713. (Table-I)

At 1 year post-induction therapy, 24 hours urinary protein was 0.89±0.98 g/dl in MMF group while 2.34±1.57 g/dl in CYC group with p value of 0.0000006. Post-induction serum creatinine in MMF group was 63.65±6.77 mmol/L while in CYC group was 81.22±18.03 with p value of 0.000002. Post-induction hematuria in MMF group was in 14 (45%) patients and in CYC group it was in 13 (42%) patients with p value of 0.7978. Post-induction C3 level in MMF group was 0.52±0.01 while in CYC group was 0.54±0.1 with p value of 0.04482. Post-induction C4 level was in MMF group was 0.07±0.01 while in CYC group was 0.22±0.27 with p value of 0.00186. (Table-II)

Parameters	MMF Group	CYC Group	P-Value
Age (years)	39.68±5	37.45±4.87	0.0276
Female, n (%)	29 (94%)	30 (97%)	
Male, n (%)	2 (6%)	1 (3%)	
24 hrs urinary protein (g)	3.65±1.08	3.65±0.36	0.4938
Serum creatinine (mmol/dL)	74.88±7.55	78.98±9.29	0.000029
Hematuria, n (%)	17 (55%)	16 (52%)	0.7990
C3 level (g/l)	0.48±0.09	0.48±0.09	0.4188
C4 level (g/l)	0.13±0.17	0.11±0.06	0.2713

Table-I. Pre-induction therapy characteristics of the participants

Parameters	MMF Group	CYC Group	P-Value
24 hrs urinary protein (g)	0.89±0.98	2.34±1.57	0.0000006
Serum creatinine (mmol/dL)	63.65±6.77	81.22±18.03	0.000002
Hematuria, n (%)	14 (45%)	13 (42%)	0.7978
C3 level (g/l)	0.52±0.01	0.54±0.1	0.04482
C4 level (g/l)	0.07±0.01	0.22±0.27	0.00186

Table-II. Post-induction therapy characteristics of the participants at 1 year

At 1 year of induction therapy, complete renal remission (CRR) in MMF group was observed in 24 (77%) patients while in CYC group it was observed in 9 (29%) patients with p value of 0.000135. Partial renal remission (PRR) in MMF group was observed in 5 (16%) patients while in CYC group it was observed in 5 (16%) patients. Total renal remission (TRR) in MMF group was observed in 29 (94%) patients while in CYC group it was observed in 14 (45%) patients with p value of 0.000036. (Figure-1)

Post treatment different complications were observed in 16 (52%) patients in MMF group

while in all 26 (83.9%) patients in CYC group. Leucopenia was present in 1 (3%) patient in MMF group and in 2 (6%) in CYC group with p value of 0.5539. Alopecia was present in 3(10%) in MMF group & in 3 (10%) patients in CYC group with p value of 1.000. Infections were observed in 8 (26%) patients in MMF group & in 9 (29%) patients in CYC group with p value of 0.7759. GI disturbances were observed in 4 (13%) in MMF group & in 12 (39%) patients in CYC group with p value of 0.020237. (Figure-2).

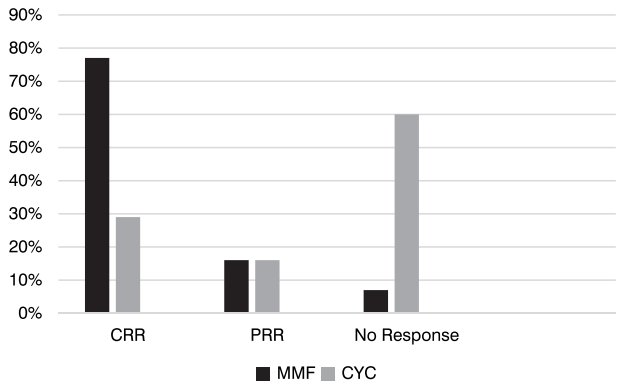

Figure-1. Renal remission in both treatment groups 1 year after induction

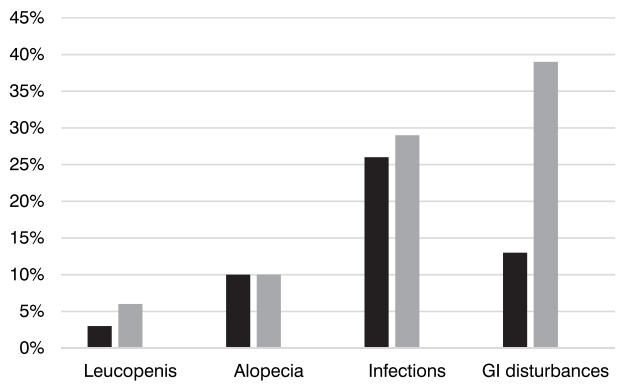

Figure-2. Post treatment complications at 1 year

DISCUSSION

SLE is actually a long term state which brings along a huge burden of complications with it while also leaving a high risk of death. Lupus nephritis is a type of SLE complication that involves the kidney and offers very grim prospects for the patient, should diagnosis fail to be made, or start treatment is put on hold at an early state. Cyclophosphamide has been considered as the standard for treating lupus nephritis, yet serious side effects and limited effectivity have led to the search for alternative therapies. Supported by previous reports of successful outcomes with mycophenolate mofetil for high-risk lupus nephritis patients with poor prognosis, we proposed that mycophenolate mofetil could be superior in efficacy to intravenous cyclophosphamide in achieving remission of active nephritis.[12] We also assumed it might be better tolerated by patients with fewer adverse effects.

Attaining renal remission post-induction therapy has been established to correlate with better long-term kidney survival. Multiple observational studies as well as randomized trials have reported that Mycophenolate Mofetil (MMF) is at least as effective as low-dose intravenous Cyclophosphamide (CYC) but with fewer side effects.[12-18]

The very first study comparing the efficacy of MMF versus CYC in the treatment of proliferative lupus nephritis (LN) came to light in the year 2000. The research further revealed that complete renal response (CRR) was attained within a year by 81% of patients receiving MMF while 14% had partial renal response (PRR). In comparison, the group receiving CYC followed by azathioprine had CRR in 76%, and PRR in 14%.[19] This finding underscored the role that MMF might play in achieving remission in LN, a hypothesis later confirmed by several other studies.[6,18,20-21] In a global randomized controlled trial with approximately 370 LN patients, after a period of 24 weeks, 56.2% of patients treated with MMF and 53.0% of those receiving intravenous CYC reached the primary efficacy endpoint.[6] Some researchers have even suggested that MMF could be more effective than CYC in inducing remission for LN.[14,22] In a meta-analysis of controlled trials with 1,989 patients suffering from lupus nephritis (LN): mycophenolate mofetil (MMF) was found to be superior to cyclophosphamide (CYC). Indeed, this medication presented a greater complete remission rate (CRR) as well as an increase in C3 levels compared to that obtained with CYC.[23]

In our setting we evaluated and compared the effectiveness and safety of MMF versus CYC in

our study. There was little difference between the two groups regarding the baseline characteristics of the patients. Our results have found the renal remission rates among patients with LN treated with MMF is much better than those treated with CYC. These findings are relatively similar to those from prior studies. The MMF group achieved significantly higher rates of TRR and CRR at 1 year compared with the CYC group. MMF-treated patients had lower 24-hour urinary protein levels, lower serum creatinine values, and lower immune mediators' levels as compared with patients in CYC group. These all finding were statistically significant. Similarly less number of complications were encountered in MMF group post therapy as compared to CYC group. Our findings in all these aspects are similar to the findings presented by similar studies conducted in the past.[10,14,24]

CONCLUSION

MMF is more affective as induction therapy for lupus nephritis as compared to IV CYC. Moreover it is more safe and tolerable.

LIMITATIONS

Our study is a single center prospective cohort study, where there are chances of bias. So, multi-center randomized trials are recommended. Similarly, the sample size of our study was low as compared to previous published studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Gasparotto M, Gatto M, Binda V, Doria A, Moroni G. **Lupus nephritis: clinical presentations and outcomes in the 21st century.** Rheumatol (Oxford). 2020; 59(Suppl5):v39-v51.

2. Parikh SV, Almaani S, Brodsky S, Rovin BH. **Update on Lupus Nephritis: Core Curriculum 2020.** Am J Kidney Dis. 2020; 76:265-81.

3. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. **2019 update of the EULAR recommendations for the management of systemic lupus erythematosus.** Ann Rheum Dis. 2019; 78(6):736-45.

4. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. **Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases.** Kidney Int. 2021; 100(4):753-79.

5. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. **American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis.** Arthritis Care Res (Hoboken). 2012; 64(6):797-808.

6. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. **Aspreva Lupus Management Study Group. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis.** J Am Soc Nephrol. 2009; 20(5):1103-12.

7. Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al. **2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis.** Ann Rheum Dis. 2020 Jun; 79(6):713-23.

8. Henderson L, Masson P, Craig JC, Flanc RS, Roberts MA, Strippoli GF, et al. **Treatment for lupus nephritis.** Cochrane Database Syst Rev. 2012 Dec 12; 12:CD002922.

9. Cassia MA, Alberici F, Jones RB, Smith RM, Casazza G, Urban ML, et al. **Rituximab as Maintenance Treatment for Systemic Lupus Erythematosus: A Multicenter Observational Study of 147 Patients.** Arthritis Rheumatol. 2019 Oct; 71(10):1670-80.

10. Saeed MA, Khan A, Naeem F, Ahmad NM. **Mycophenolate mofetil vs. cyclophosphamide-based induction regimens for lupus nephritis: Outcomes at a tertiary care centre in Lahore, Pakistan.** J Pak Med Assoc. 2024; 74(5):868-73.

11. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, et al. **Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis.** Ann Rheum Dis. 2012; 71:1771-82.

12. Medina-Rosas J, Fung WA, Su J, Touma Z. **Effect of complete or partial proteinuria recovery on longterm outcomes of lupus nephritis.** Semin Arthritis Rheum. 2018; 47(4):557-64.

13. Korbet SM, Lewis EJ, **Collaborative Study G. Severe lupus nephritis: the predictive value of a[/= 50% reduction in proteinuria at 6 months.** Nephrol Dial Transplant. 2013; 28(9):2313-8.

14. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. **Mycophenolate mofetil orintravenous cyclophosphamide for lupus nephritis.** N Engl J Med. 2005; 353(21):2219-28.

15. 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):235-42.

16. Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, et al. **Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis.** Nephrol (Carlton). 2005; 10(5):504-10.

17. Wang J, Hu W, Xie H, Zhang H, Chen H, Zeng C, et al. **Induction therapies for class IV lupus nephritis with non-inflammatory necrotizing vasculopathy: mycophenolate mofetil or intravenous cyclophosphamide.** Lupus. 2007; 16(9):707-12.

18. Gadakchi L, Hajialilo M, Nakhjavani MR, Azar SA, Kolahi S, Gojazadeh M, et al. **Efficacy and safety of mycophenolate mofetil versus intravenous pulse cyclophosphamide as induction therapy in proliferative lupus nephritis.** Iran J Kidney Dis. 2018; 12(5):288-92.

19. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al. **Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group.** N Engl J Med. 2000; 343(16):1156-62.

20. El-Shafey EM, Abdou SH, Shareef MM. **Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients?** Clin Exp Nephrol. 2010; 14(3):214-21.

21. Mak A, Cheak AA, Tan JY, Su HC, Ho RC, Lau CS. **Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: A meta-analysis and metaregression.** Rheumatol (Oxford). 2009; 48(8):944-52.

22. Elliott JR, Manzi S. **Induction therapy for active lupus nephritis: mycophenolate mofetil is superior to cyclophosphamide.** Nat Clin Pract Rheumatol. 2006; 2(7):354-5.

23. Jiang YP, Zhao XX, Chen RR, Xu ZH, Wen CP, Yu J. **Comparative efficacy and safety of mycophenolate mofetil and cyclophosphamide in the induction treatment of lupus nephritis: A systematic review and meta-analysis.** Med (Baltimore). 2020; 99(38):e22328.

24. Zhang X, Huang H, Gao D, Zhao J, Ji L, Fan Y, et al. **Comparison of the effectiveness and safety of mycophenolate mofetil and cyclophosphamide in lupus nephritis: Evidence from a real-world study.** Rheumatol Ther. 2023; 10:1199-213.

AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Maimoona Firdus:** Conception of study, design, data collection, analysis, interpretation, drafting.
2	**Rashid Usman:** Data collection, discussion writing.
3	**Maryam Ahmed:** Data collection, discussion writing.
4	**Saira Yasmin:** Conception of study design, data collection, analysis and interpretation, drafting, final approval of the version.
5	**Shahida Parveen:** Conception of study design, data collection, analysis and interpretation, drafting, final approval of the version.
6	**Babur Salim:** Conception of study, design, data collection, analysis and interpretation, drafting.