# Efficacy and Safety of Mycophenolate Mofetil Versus Intravenous Pulse Cyclophosphamide as Induction Therapy in Proliferative Lupus Nephritis

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**Introduction.** Lupus nephritis is a common and severe manifestation of systemic lupus erythematosus that can lead to end-stage renal disease and death. The aim of this study was to compare the efficacy and safety of mycophenolate mofetil (MMF) and cyclophosphamide as induction therapy and subsequently as maintenance therapy for lupus nephritis.

**Materials and Methods.** In this retrospective case-control study, 67 patients with proliferative lupus nephritis who were treated with MMF (n = 45) and pulse of intravenous cyclophosphamide (n = 22) were included. Remission of the kidney disease, mortality, and adverse events were evaluated and compared between the two groups.

**Results.** The 45 patients treated with MMF had a mean age of 33.8 ± 10.6 years and 17.1% of them were males. The 22 patients treated with pulse of intravenous cyclophosphamide had a mean age of 38.1 ± 11.1 years and 18.2% of them were males. Complete and partial kidney remission occurred in 40% and 42.2% of the patients treated with MMF and in 31.8% and 59.1% of the patients treated with cyclophosphamide, respectively. No significant differences were observed in complete and partial remission between the two groups. No mortality was reported in the studied patients. There were no significant differences in the frequency of adverse events between the two groups.

**Conclusions.** The efficacy of MMF in long-term treatment of lupus nephritis was comparable to that of cyclophosphamide, and there is no significant differences in the rate of side effects between the two regimens.

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## INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that involves various organs and has several manifestations.[1] Lupus nephritis is a common and severe manifestation of SLE that can lead to end-stage renal disease and death.[2] Lupus nephritis occurs in up to 60% of adults with SLE and predicts poor survival. The prevalence of SLE and lupus nephritis and treatment response vary by age, sex, and race or ethnicity.[2,3] In the past 20 years, treatment of lupus nephritis has advanced significantly, and induction therapies that combine cyclophosphamide and corticosteroids have improved renal outcomes compared with

treatment with steroids alone.[4,5]

In recent years, there has been an increased interest in immunosuppressive agents used in solid organ transplantation. Evidence from early observational studies suggested that these medications might be efficacious in inducing remission of lupus nephritis.[6] Mycophenolate mofetil (MMF), an immunosuppressive agent that has been demonstrated to be safe and effective in treatment of lupus nephritis.[6] Several randomized controlled trials comparing MMF and cyclophosphamide as induction agents in lupus nephritis have shown that MMF is as effective as cyclophosphamide and may offer advantages over cyclophosphamide.[6-9] The aim of this study was to compare the efficacy and safety of MMF and cyclophosphamide as induction therapy and subsequently as maintenance therapy for lupus nephritis.

## METHODS AND MATERIALS

This retrospective case-control study was carried out on 67 patients with proliferative lupus nephritis who had been monitored from 2007 to 2017 at the lupus clinic of Connective Tissue Diseases Research Center. Inclusion criteria were diagnosis of SLE according to the American College of Rheumatology criteria,[10] diagnosis of lupus nephritis according to the World Health organization criteria,[11] and renal biopsy and receiving pulses of monthly intravenous cyclophosphamide or MMF. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences.

Based on the Connective Tissue Diseases Research Center protocol, patients were treated with prednisolone, 1 mg/kg/day, and if patients had high levels of creatinine, pulse of methylprednisolone, 1 g/d for 3 consecutive days, and then prednisolone, 1 mg/kg/d, were initiated. After controlling the disease, prednisolone dose was reduced gradually. Mycophenolate mofetil was prescribed orally at the dose of 2 g/d. The dose of MMF was reduced when the prednisolone dose fell below 7.5 mg/d and the remission lasted for 1.5 to 2 years. Cyclophosphamide was used as monthly pulses of 1 g for 4 to 6 months and after getting remission was replaced with azathioprine or MMF. Disease activity, dose of steroids used, remission of the kidney disease, and involvement of other organs, dialysis, kidney transplantation, mortality, and adverse events, as well as laboratory measurements including complete blood count, serum urea, serum creatinine, C-reactive protein, erythrocyte sedimentation rate, serum liver enzymes, serum complement, anti–double-stranded DNA, urinalysis, 24-hour urine protein, 24-hour urine creatinine, were evaluated at baseline and every 3 months during follow-up. Disease activity was measured by SLE disease activity index, in which scores above 7 were considered active disease. Criteria for remission of the kidney disease are presented in Table 1.

Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA). All variables were normally distributed as tested by the Kolmogorov-Smirnov test. Categorical variables were expressed as numbers (percentages) and were compared using the chi-square or the Fisher exact test. Quantitative variables were displayed as mean ± standard deviation. The differences between variables before and after treatment were compared

**Table 1.** Criteria for Remission of Kidney Disease

| Condition | Criteria |
|---|---|
| Complete kidney remission | All of the following criteria present:<br>- Proteinuria < 300 mg/d<br>- Normal urinary sediment<br>- Both serum creatinine concentration and creatinine clearance 15% or less above the baseline values<br>- Normal serum albumin concentration |
| Partial kidney remission | All of the following criteria present:<br>- Reduction of proteinuria to 300 mg/d to 2900 mg/d and at least 50% reduction in proteinuria if the baseline proteinuria was more than 3 g/d<br>- Stabilization of kidney function (change in serum creatinine concentration of less than 20% compared with the baseline concentration) or improvement in kidney function (reduction in serum creatinine concentration of at least 20% compared with the baseline)<br>- Urinary erythrocytes < 10 per high power field<br>- Serum albumin ≥ 3 g/dL |

by the paired *t* test. Between-group comparisons were made by independent sample *t* test. *P* values less than .05 were considered significant.

## RESULTS

In this study, 67 patients who were treated with MMF (n = 45) and pulse of intravenous cyclophosphamide (n = 22) were included. Demographic, clinical, and laboratory findings of patients are shown in Table 2. Follow-up duration in the cyclophosphamide group was significantly more than MMF group. Complete and partial renal remission occurred in 40.0% and 42.2% of the patients treated with MMF and in 31.8% and 59.1% of the patients treated with cyclophosphamide, respectively (Table 3). Differences were not significant. No end-stage renal failure or mortality was reported in studied patients. Table 3 presents frequency of adverse events in the studied patients. Infections and abortion were the most common

**Table 2.** Baseline Characteristics of Studied Patients*

| Parameters | Mycophenolate Mofetil Group (n = 45) | Cyclophosphamide Group (n = 22) | *P* |
|---|---|---|---|
| Age, y | 32.3 ± 10.1 | 29.8 ± 10.2 | > .05 |
| Sex | | | |
| Female | 50 | 26 | |
| Male | 11 | 6 | > .05 |
| Disease duration, y | 3.6 ± 2.8 | 3.5 ± 2.4 | > .05 |
| Follow-up duration, mo | 37.2 ± 9.8 | 75.1 ± 15.8 | .006 |
| Lupus nephritis class III | 13 (28.9) | 5 (22.7) | > .05 |
| Lupus nephritis class IV | 32 (71.1) | 17 (77.3) | > .05 |

*Values are mean ± standard deviation or frequency (percentage).

**Table 3.** Treatment Results in Studied Patients*

| Parameters | Before Treatment | | | End of Follow-up | | |
|---|---|---|---|---|---|---|
| | Mycophenolate Mofetil | Cyclophosphamide | *P* | Mycophenolate Mofetil | Cyclophosphamide | *P* |
| Constitutional symptoms | 18 (40) | 10 (45.6) | > .05 | 3 (6.7) | 1 (4.5) | > .05 |
| Skin lesions | 17 (37.8) | 8 (36.4) | > .05 | 6 (13) | 1 (4.5) | > .05 |
| Arthralgia/arthritis | 24 (53.3) | 8 (36.4) | > .05 | 11 (24.4) | 3 (13.6) | > .05 |
| Hematologic involvement | 26 (57.4) | 14 (63.6) | > .05 | 26 (57.4) | 14 (63.6) | > .05 |
| Azotemia | 10 (22.2) | 6 (45.5) | > .05 | 5 (11.1) | 4 (18.1) | > .05 |
| Serositis | 4 (8.9) | 4 (18.2) | > .05 | 1 (2.2) | 0 | … |
| Severe cardiopulmonary involvement | 2 (4.4) | 2 (9.1) | > .05 | 0 | 0 | … |
| Central nervous system involvement | 0 | 2 (9.1) | > .05 | 0 | 1 (4.5) | … |
| Vasculitis | 3 (6.7) | 4 (18.2) | > .05 | 0 | 0 | … |
| SLE disease activity index | 12.4 | 14.6 | .02 | 4.2 ± 2.3 | 3.7 ± 2.1 | > .05 |
| Prednisolone dose | 26.5 ± 15.9 | 43 ± 16.8 | .001 | 10.5 ± 9.1 | 10.3 ± 7.8 | > .05 |
| Complete renal remission | … | … | … | 18 (40) | 7 (31.8) | > .05 |
| Partial renal remission | … | … | … | 19 (42.2) | 13 (59.1) | > .05 |
| No renal remission | … | … | … | 8 (17.8) | 2 (9.1) | > .05 |
| End stage renal failure | … | … | … | 0 | 0 | … |
| Changing treatment regimen | … | … | … | 10 (22.2) | 4 (18.2) | > .05 |
| Treatment complications | | | | | | |
| Infection | … | … | … | 3 (6.7) | 1 (4.5) | |
| Abortion | … | … | … | 3 (6.7) | 3 (13.6) | |
| Amenorrhea | … | … | … | 0 | 0 | |
| Infertility | … | … | … | 0 | 0 | |
| Bone marrow suppression | … | … | … | 0 | 0 | |
| Others | … | … | … | 1 (2.2) | 1 (4.5) | > .05 |
| Mortality | … | … | … | 0 | 0 | … |

*Values are mean ± standard deviation or frequency (percentage).

side effects. Abortion occurred in 3 patients in each group. All of them were spontaneous. As indicated in Table 3, there were no significant differences in frequency of adverse events between the two groups.

## DISCUSSION

Lupus nephritis is one of the most severe manifestations of SLE associated with considerable morbidity and mortality. Various organs such as the kidney, lung, and nervous system are involved in this disease.[12,13] Different treatment regimens have been suggested for lupus nephritis. Immunosuppressive regimens of glucocorticoids combined with cytotoxic drugs, particularly cyclophosphamide, are effective for the treatment of severe proliferative lupus nephritis.[12-14] However, cyclophosphamide is associated with adverse events such as bone marrow suppression, amenorrhea and sterility, increased risk of infections, hemorrhagic cystitis, bladder cancer, leukemias, and other malignancies. Therefore, a safer yet effective alternative therapy is needed. Mycophenolate mofetil is a relatively specific inhibitor of lymphocyte proliferation and has been effective in reducing the acute rejection rate in renal transplantation.[4-6,12,13] In murine models of lupus nephritis, MMF attenuates the severity of kidney disease and significantly prolongs survival.[14] Evidence from early observational studies suggested that these drugs might be efficacious in inducing remission of lupus nephritis. Mycophenolate mofetil has been demonstrated to be safe and effective in treatment of patients with lupus nephritis.[15]

According to our results, no significant differences were observed in complete and partial renal remission) between the two groups. Similar to our findings, Mak and colleagues[15] reported no significant differences in remission of the kidney disease between patients treated with MMF and cyclophosphamide. In another study, Ginzler and colleagues[3] indicated that complete renal remission occurred in 22% and 5% of patients treated with MMF and cyclophosphamide, respectively, which was in contrast with present study. Furthermore, treatment failure was reported in 47% and 69% of patients treated with MMF and cyclophosphamide, respectively,[3] which was higher than our study. In another study, Appel and coworkers[7] reported that treatment with MMF and cyclophosphamide was successful in 56% and 53% of patients, respectively, and concluded that both drugs had the same efficacy in inducing remission in lupus nephritis, which was consistent with the present study.

One of the important aspects of therapy is side effects. One of the important adverse events of therapy with cyclophosphamide and MMF is infections such as pneumonia.[3] Although side effects associated with MMF are fewer, gastrointestinal side effects may occur more frequently.[3] Based on Ginzler and colleagues' study,[3] gastrointestinal side effects, infection, and leukopenia were among the most common adverse events associated with MMF and cyclophosphamide. Furthermore, severe infection occurred in 6 patients treated with cyclophosphamide, whilst gastrointestinal side effects particularly diarrhea were more common in patients treated with MMF.[3] In another study by Dooley and coworkers,[16] only limited side effects and in some cases asymptomatic leukopenia and pancreatitis in only one case had been reported in patients treated with MMF. Moreover, Appel and coworkers[7] reported no significant differences in adverse events between patients treated with MMF and cyclophosphamide, which was consistent with present study. In contrast with our study, Conteras and coworkers[17] indicated high frequency of severe infection (25%), amenorrhea and leukopenia in patients treated with cyclophosphamide.

Despite previous reports regarding high frequency of infection in patients treated with cyclophosphamide, infections occurred in 3 and 1 patients in the MMF- and cyclophosphamide-treated groups, respectively. Neither MMF nor cyclophosphamide had an adverse impact on patients' reproductive status. Furthermore, no sterility was observed in our study and abortion occurred in only 3 patients in both MMF and cyclophosphamide groups. Taking into account that there was no endocarditis, myocarditis, alveolar hemorrhage, cerebritis, cerebrovascular accident, seizures, and hemolysis in our patients, we concluded that organ involvement was negligible in the present study. In addition, despite Ginzler and colleagues,[3] who reported leukopenia as the most common side effect, bone marrow suppression was not observed in patients treated with MMF and was found in only one patient in cyclophosphamide group. According to Hu and associates,[9] gastrointestinal side effects and infection occurred in 26% and 17.4% of patients treated with

MMF and in 43% and 30.4% of patients treated with cyclophosphamide, respectively. This study indicated positive effects of MMF compared to cyclophosphamide in treatment of lupus nephritis with fewest adverse events. In contrast with Hu and associates' study,[9] gastrointestinal side effects were not observed in patients treated with MMF and infection was found in only 1 patient treated with cyclophosphamide in our study.

## CONCLUSIONS

The efficacy of MMF in long-term treatment of lupus nephritis is comparable to that of cyclophosphamide, and there is no significant differences in the rate of side effects between the two regimens.

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## CONFLICT OF INTEREST

None declared.

## REFERENCES

1. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR. Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2007;2:968-75.
2. Flanc RS, Roberts MA, Strippoli GF, Chadban SJ, Kerr PG, Atkins RC. Treatment of diffuse proliferative lupus nephritis: A meta-analysis of randomized controlled trials. Am J Kidney Dis. 2004;43:197-208.
3. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis. N Engl J Med. 2005;353:2219-28.
4. Boumpas DT, Austin HA III, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part I. Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. Ann Intern Med. 1995;122;940-50.
5. Valeri A, Radhakrishnan J, Estes D, et al. Intravenous pulse cyclophosphamide treatment of severe lupus nephritis: a prospective five-year study. Clin Nephrol. 1994;42:71-8.
6. Kapitsinou PP, Boletis JN, Skopouli FN, Boki M. Lupus nephritis: treatment with Mycophenolate Mofetil. Rheumatology. 2004;43:377-80.
7. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis. J Am Soc Nephrol. 2009;20:1103-12.
8. Rathi M, Goyal A, Jaryal A, et al. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. Kidney Int. 2016;89:235-42.
9. Hu W, Liu Z, Chen H, et al. Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chinese Med J. 2002;115:705-9.
10. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271-7.
11. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004;15:241-50.
12. Grande JP. Experimental models of lupus nephritis. Contrib Nephrol. 2011;169:183-97.
13. Borchers AT, Leibushor N, Naguwa SM, et al. Lupus nephritis: a critical review. Autoimmun Rev. 2012;12:174-94.
14. Corna D, Morigi M, Facchinetti D, et al. Mycophenolate Mofetil Limits renal damage and prolongs life in murine lupus autoimmune disease. Kidney Int. 1997;51:1533-9.
15. Mak A, Cheak AAC, Tan JYS, Cho SH, Ho RCM, Sing LC. Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression. Rheumatology. 2009;48:944-52.
16. Dooley MA, Cosio FG, Nachman PH, et al. Mycophenolate Mofetil Therapy in Lupus Nephritis: Clinical Observations. J Am Soc Nephrol. 1999;10:833-9.
17. Conteras G, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;10:971-80.

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