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Research Article

EFFICACY OF MYCOPHENOLATE MOFETIL VERSUS CYCLOPHOSPHAMIDE IN THE TREATMENT OF LUPUS NEPHRITIS

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ABSTRACT

Objective: Despite the prevalence of SLE, lupus nephritis (LN) is the primary cause of morbidity and mortality. This study objective was to assess the efficacy and safety of the induction treatment with mycophenolate mofetil (MMF) and cyclophosphamide (CYC).

Methods: This was a prospective observational study enrolled 100 LN patients who were treated with MMF and cyclophosphamide. In this study, 6 male and 44 female patients were treated with MMF and 3 male and 47 female patients were treated with cyclophosphamide. To estimate drug efficacy, patients were evaluated for 24-h urinary protein excretion estimation, serum creatinine, protein-creatinine ratio (PCR), Proteinuria, Serum complement C_3, Serum complement C_4, and Serum albumin. The primary end point was a prespecified decrease in urine PCR and stabilization of serum creatinine. Secondary end points were complete renal remission, systemic disease status and safety.

Results: The results indicated a potential small advantage of MMF over CYC although the results were not significant. Serum creatinine, 24-h urine protein, and serum albumin were also similar between the MMF and CYC groups after induction therapy. Leukopenia was significantly reduced in MMF treated patients. Both groups suffered from upper gastrointestinal symptoms, but the MMF group's symptoms were mild and self-limited. MMF therapy was effective in reducing proteinuria and boosting serum complement levels.

Conclusion: MMF and CYC were not significantly different in remission induction therapies for LN. Clinical improvement was seen in most patients in both treatment groups.

Keywords: Lupus nephritis, Systemic lupus erythematosus, Mycophenolate mofetil, Cyclophosphamide, Protein-creatinine ratio, Efficacy, Observational study, Serum complements C_3 & C_4.

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INTRODUCTION

As one of the most severe manifestations of systemic lupus erythematosus (SLE), lupus nephritis (LN) is an autoimmune disease may get worse over time and lead to kidney failure [1]. LN is caused by the deposition of anti-double stranded DNA antibodies (anti-dsDNA) in glomerular basement membrane. It is a potentially life-threatening disease with a 60% mortality rate in adults with SLE [2].

Most SLE patients develop nephritis early in the course of their disease. The treatment of LN consists of an induction phase and a maintenance phase to prevent relapse and progression to end-stage renal disease [3] According to the LN management guidelines proposed by the ACR, European League Against Rheumatism (EULAR), and kidney disease improving global outcomes patients with active LN are recommended to take IVC or MMF in combination with oral glucocorticoids, with or without three pulses of intravenous methylprednisolone at the start of remission induction therapy. After remission is obtained, maintenance therapy with a tapering dose of corticosteroids is combined with an antimetabolite (mycophenolate or azathioprine) [4]. LN has been treated with glucocorticoids and CYC for more than two decades, but its efficacy in severe cases is still unsatisfactory, and there are obvious side effects such as suppressed bone marrow and gonadal function.

Mycophenolate mofetil (MMF) is a "Prodrug" of mycophenolic acid (MPA) a potent and reversible inhibitor of inosine monophosphate dehydrogenase which has become a target for immunosuppression since lymphocytes depend on the *de novo* guanosine nucleotide synthesis to reduce the accumulation of circulating immune complex in renal tissue [5].

Cyclophosphamideis an alkylating agent has immunosuppressive effects and is selective for T cells. It has been used extensively to treat severe manifestations of a variety of autoimmune and inflammatory diseases. Examples include organ-threatening manifestations of rheumatic diseases such as systemic lupus erythematosus (SLE). An important effect of cyclophosphamide is the reduction of antinuclear antibody levels and the proliferation of glomerular cells, as well as the decrease in immunoglobulin staining in glomeruli. Progression of glomerulosclerosis was significantly arrested [6].

METHODS

Study site

It was a prospective observational study conducted on LN patients at Arun kidney centre, Suryaraopet, Vijayawada, NTR District and Andhra Pradesh to compare the efficacy of MMF and cyclophosphamide.

Study design

The study was approved by the Institutional Ethics Committee with the reference number IEC-ASNPC/2020-21/APPROVAL-1. Written informed consent was provided to each patient typically over the age of 18. The study procedures were conducted in accordance with the ethical principles of Helsinki and its amendments with the CDSCO recommendations, Indian Council of Medical Research and GCP guidelines.

Study period

March–August 2021.

Inclusion criteria

The following criteria were included in the study:

1. Patients with biopsy proven LN.
2. 18–65 years of both male and female.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients who were not under regular follow-up.
2. Pregnant and lactating women.

Out of 120 patients, 100 patients met inclusion criteria requirements.

Study protocol

Patients who received one of the two treatments (MMF or i.v. CYC) were followed-up over a period of 6 months. Their records were perused and relevant data obtained for comparison.

MMF group

Patients in the MMF group received oral MMF 500 mg T.i.d.

CYC group

Patients in the CYC group received cyclophophamide500 mg injection I.V. 6 doses/month. All patients had received unified concomitant corticosteroid therapy prednisolone 40 mg once daily. Dosage was maintained till the end of 6 months.

RESULTS

This was a prospective observational study with 100 LN patients who were under treatment with either MMF or cyclophosphamide. In this study, 6 males and 44 females were treated with MMF and 3 males and 47 females were treated with cyclophosphamide. These patients were evaluated for tests like serum creatinine, PCR, proteinuria, serum complement C_3, serum complement C_4, and serum albumin for estimating the drug efficacy (Table 1).

The previous studies have shown that women account for the majority of SLE cases, with a female: male ratio of approximately 7:1–9:1. There is conflicting evidence that women with SLE have increased estrogen levels, which have immunomodulatory functions including differences in inflammatory cytokine production and both B- and T-cell activation could be impact blood pressure, although the connection between these factors in patients with SLE has not been well studied (Fig. 1) [7].

Lupus is an autoimmune disease that can happen both in adults and children. Typically the mean age of SLE onset ranges 35–45 years old. Women of all ages are affected far more than men. Incidence, prevalence, and epidemiology of SLE and variation with age, sex, ethnicity, and time (Fig. 2) [8].

The risk of comorbidities was elevated especially in renal diseases. Hypertension is more common in LN patients [9]. Impaired renal function is certain to contribute to the prevalent hypertension in SLE patients. Arterial hypertension burden up to two third of systemic lupus erythematous (SLE) patients and contributes to accelerated atherosclerosis and cardiovascular (CV) risk (Fig. 3) [10].

The upper gastrointestinal symptoms were common in two groups. In MMF group the symptoms to be mild and self-limited whereas in the cyclophosphamide group dehydration following moderate GI symptoms. Leukopenia occurred significantly less frequent in MMF group. Hives (Urticaria) were not significantly different between the two groups. The MMF group tends to have low muscle spasms, drug induced infections than the cyclophosphamide group, but this effect was not significant. The overall adverse effects were not significantly different between the groups except leukopenia (Table 2) [11].

Elevated creatinine level indicates impaired kidney function. Compared to the Cyclophosphamide group, the Mycophenolate group's serum creatinine level decreased considerably. This shows that MMF was effective in lowering serum creatinine levels (Table 3) [12].

Table 1: Gender-wise distribution of total lupus nephritis patients

Gender	Male	Female
Mycophenolate mofetil	6	44
Cyclophosphamide	3	47
Total	9	91

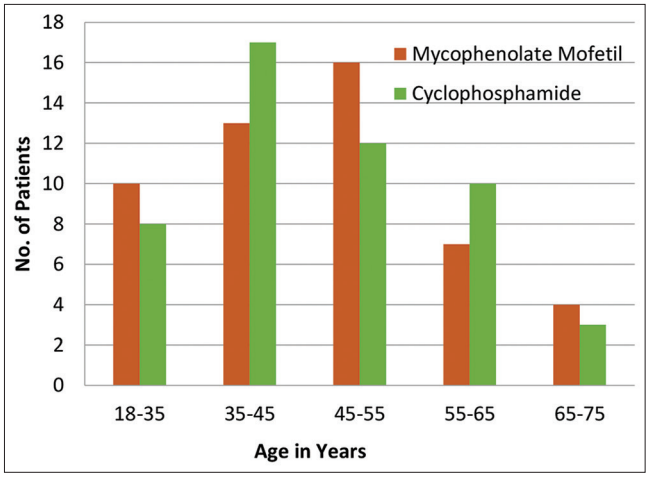

Fig. 1: Age distribution of total lupus nephritis patients

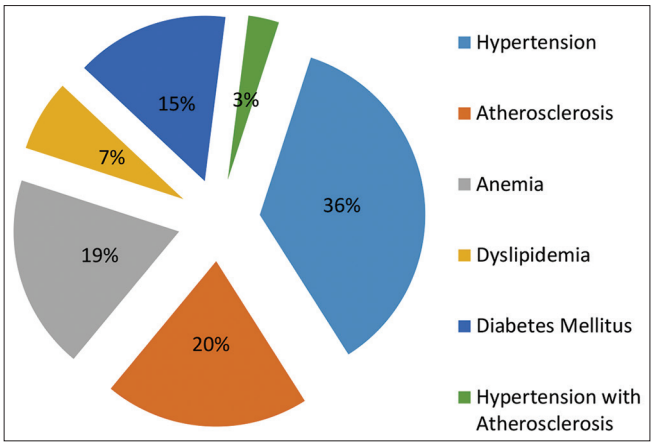

Fig. 2: Comorbidities in lupus nephritis patients

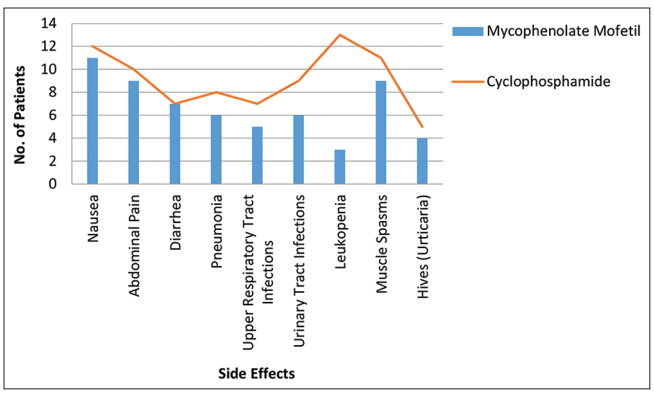

Fig. 3: Side effects in LN patients using mycophenolate mofetil versus cyclophosphamide

Table 2: Average serum creatinine level in total sample size

Average Creatinine	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Mycophenolate Mofetil	1.64	1.53	1.40	1.32	1.23	1.15
Cyclophosphamide	1.65	1.56	1.51	1.44	1.37	1.30

Table 3: Average serum albumin level in total sample size

Average serum albumin	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Mycophenolate mofetil	2.81	3.02	3.26	3.44	3.65	3.84
Cyclophosphamide	2.74	2.93	3.15	3.32	3.51	3.69

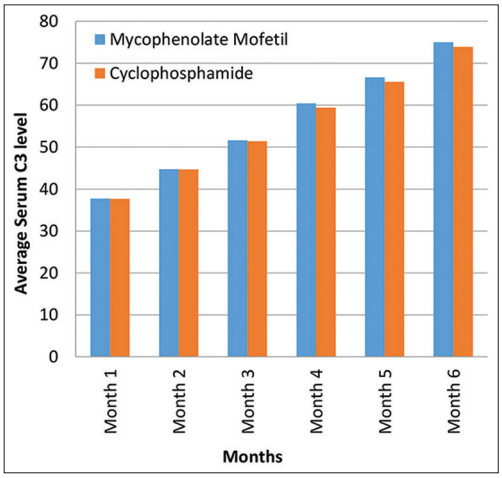

Fig. 4: Average serum complement C_3 level in total sample size

Serum albumin (SA), the most prevalent circulatory protein is linked to numerous essential physiological activities. Low serum albumin levels may be a sign of a liver, kidneys, or other health conditions. There was no discernible difference between MMF and cyclophosphamide in response to reduce serum albumin levels (Fig. 4) [13].

The complement system, which is a component of the immune system, contains more than 30 distinct proteins. They operate sequentially and provide infection prevention. Lupus patients usually have low C_3 and C_4 levels during disease flare-ups due to activation of the complement system by immune complexes. Serum complement C3 levels considerably increased in the mycophenolate group compared to the cyclophosphamide group as shown in Fig. 5 [14].

C_4 is a type of special protein that is found on the surface of certain cells and in blood plasma. It is part of over 60 proteins that supports the immune system. These complement proteins aid in the defense against viral and bacterial infections as well as other foreign material. Rare genetic mutations can lowers C4 protein levels which give a greater risk of developing infections and autoimmune diseases such as lupus, rheumatoid arthritis, and systemic sclerosis. In active lupus renal disease, both the classic and the alternate pathways of the complement cascade are activated, and serum levels of C_4 are often depressed. As per Fig. 5, serum complement C_4 level significantly increased in Mycophenolate group than in cyclophosphamide group that indicates MMF was efficient in increasing serum complement C_4 level when compared with cyclophosphamide (Fig. 6) [15].

Elevated levels of PCR values are a sign of kidney damage in which the GFR is abnormal. PCR significantly decreased in mycophenolate group than in cyclophosphamide group [16]. This indicates MMF was effective in decreasing PCR when compared to cyclophosphamide [17].

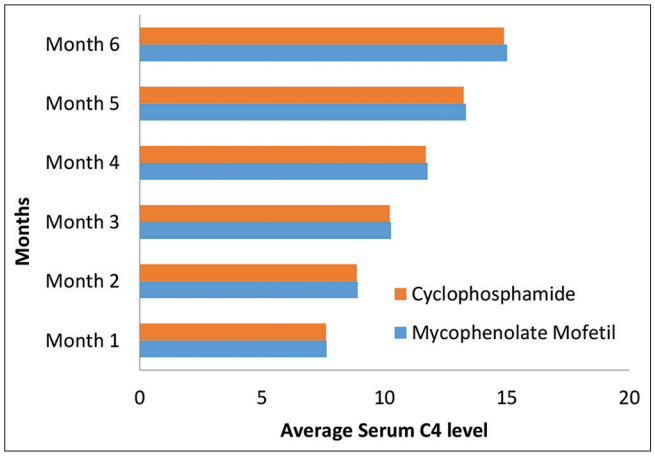

Fig. 5: Average serum complement C_4 level in total sample size

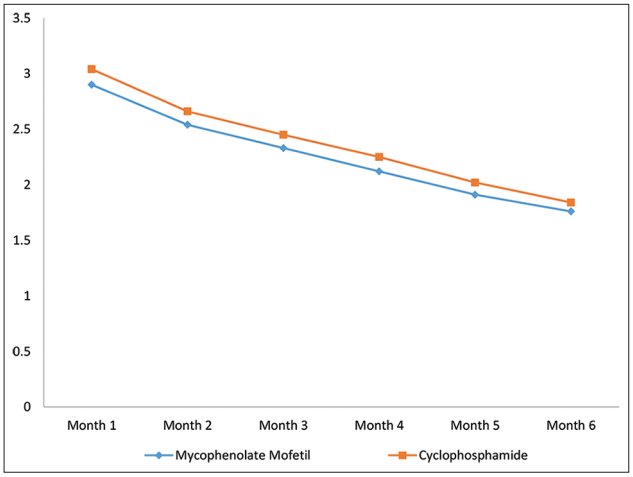

Fig. 6: Average protein creatinine ratio (PCR) values in total sample size

DISCUSSION

Six-month study conducted on 100 LN patients in which MMF was as effective as cyclophosphamide in inducing remission. Within the study, the current evidences for assessment of clinical outcomes and side effects of MMF and CYC for induction therapy of LN. Final results recommend a possible small advantage of MMF over CYC though the results were not significant. Only leukopenia was significantly less frequent (35% lower) in patients treated with MMF. Serum creatinine, 24-h urine protein, and serum albumin after induction therapy were also similar between two groups.

On the basis of anecdotal reports with MMF in LN patients shows fewer toxic effects and better acceptance by patients. Although upper

gastrointestinal symptoms were common within the two groups, in the MMF group the symptoms to be mild and self- limited, whereas in the cyclophosphamide group dehydration following moderate GI symptoms, amenorrhea and leukopenia. MMF therapy was effective in reducing proteinuria and increasing serum complement levels; however, rate of infectious complications was similar in the two treatment groups. MMF appeared to be better tolerated than cyclophosphamide.

Our study had several limitations. First, it was absolutely prospective observational study, which could limit the generalizability of the results. Second, the number of LN patients allocated to each treatment arm was comparatively small that may have failed to attain statistical significance because of the small sample size. Finally, the work was conducted at a single center in the Arun kidney center, and thus, the results may not be representative of the large population.

CONCLUSION

We found no significant differences between IVC and MMF used as remission induction therapies for LN. In other words, MMF and IVC were equally effective in terms of inducing remission of LN.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript.

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