ORIGINAL ARTICLE

A COMPARISON OF MYCOPHENOLATE MOFETIL AND CYCLOPHOSPHAMIDE AS LUPUS NEPHRITIS INDUCTION THERAPY

Haris Gul, Muhammad Salman Mushtaq, Babur Salim, Saba Samreen, Amjad Nasim, Muhammad Khan

Department of Rheumatology, Fauji Foundation Hospital Rawalpindi-Pakistan

Background: Lupus nephritis and its induction therapies are understudied subjects in rheumatology especially in our population. The objective of this study is to compare the renal response to Mycophenolate mofetil (MMF) and Cyclophosphamide (CYC) as induction therapy in the Pakistani population with lupus nephritis. **Methods:** This is a comparative retrospective study conducted at the department of rheumatology, Fauji Foundation Hospital (FFH), Rawalpindi, and the duration of the study was 1.5 years from July 2016 to December 2017. The study includes 28 patients, all females, ages between 18 to 50 years. All have biopsy proven lupus nephritis (LN). All 28 LN patients have either stage III, IV, V. They were investigated and analysed over 1.5 years. 14 patients were given MMF (2.5 gram/day) (MMF group) and 14 patients were given CYC (NIH protocol/monthly) (CYC group) for 24 weeks as induction therapy. Comparison of baseline characteristics, complete and partial renal responses to treatment was seen in the MMF and CYC groups. **Results:** Primary end point (complete response) is achieved in 6 (42.85%) in MMF group and 5 (35.71%) in the CYC group. The secondary end point (partial response) was achieved in 5 (35.71%) patients in the MMF group and 6(42.85%) in the CYC group. The difference in the cumulative probability of complete and partial response was not statistically significant between the two groups (P-0.470 for CR) and (*p*-value 0.132 for PR). **Conclusion:** Mycophenolate mofetil is a new therapy for LN and it has equal efficacy as compared to CYC for LN induction.

Keywords: Lupus nephritis; Induction therapy; Mycophenolate Mofetil; Cyclophosphamide

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INTRODUCTION

Systemic lupus erythromatosis (SLE) is a multisystem, autoimmune disease with involvement of different organs like skin, joints, kidneys and brain. It has a worldwide reported frequency range from 20 to 240 per 100,000 persons and reported incidence rates to range from 1 to 10 per 100,000 persons.[1]

SLE is diagnosed based on history, examination, and certain investigations and SLICC Classification criteria.[2] Antineutrophilic antibodies (ANA), antidsDna, anti-Ro, and anti-Smith antibodies may be positive in SLE patients.

The involvement of the kidneys in SLE deems a poorer prognosis in SLE and requires aggressive management to preserve the kidney function. About 50% of SLE patients develop clinically significant nephritis.[1] In Pakistan according to one study LN has a prevalence of 45% in SLE patients[3] and 68% in another study[4]. It is known that lupus nephritis has a higher prevalence in Blacks[5] and Indians[6] than Caucasians[7]. Despite great improvement in the management of lupus nephritis, it remains the most frequent cause of SLE related mortality. The 5, 10, and 20-year survival rates were 98.6, 98.2, and 90.5%, respectively. The leading causes of death were infection (50.0%), cardiovascular disease (20.8%) and malignancy (12.5%).[8]

Lupus nephritis presents with pedal oedema, periorbital puffiness, or in some cases, these features are very subtle or even asymptomatic and diagnosed on routine urine dipstick examination in a patient already diagnosed with SLE. Nephritis may be the initial presentation in newly diagnosed patients of SLE. Lupus nephritis (LN) is diagnosed based on renal biopsy. Renal biopsy in SLE has certain indications that include increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication), confirmed proteinuria of 1.0 gram per 24 hours, or combinations of the following, proteinuria-0.5 gram per 24 hours plus haematuria, defined as-5 RBCs per hpf or proteinuria-0.5 gram per 24 hours plus cellular casts. These features make the patient eligible for renal biopsy.[9]

Renal biopsy histopathology and immunofluorescence is done for the staging of LN. There are 6 stages of LN. The stages which need strong immunosuppressant in LN are stage III which is focal lupus nephritis, Class IV diffuse lupus nephritis, and Class V – membranous lupus nephritis.[9]

Different treatment options are used for stage III, IV, V according to recent guidelines for LN treatment.[9] That includes the National Institute of health regimen (NIH) that includes giving 750 mg/m^{2}of cyclophosphamide monthly for 6 months as induction therapy, the Eurolupus regimen in which 500 mg of Cyclophosphamide is given fortnightly for 3 months as induction therapy, and the last regimen MMF is given in a dose of 2–3 gram/day for 6 months. Along with induction drugs in the start 3 doses of 1 gram of methylprednisolone was given, with 0.5–1 mg/kg steroids (prednisolone), hydroxychloroquine (HCQ), and angiotensin converting enzyme (ACE) or aldosterone receptor antagonist (ARB) in a stable dose. This induction phase of 3 or 6 months is followed by the maintenance phase in which either azathioprine (2 mg/kg) or MMF (1–2 grams/day) is given for 3–5 years.[9]

There is a lot of international data available for the efficacy of each regimen which shows that for stage III and stage IV none of the regimens is superior to one another[10,11] except in stage V where MMF is superior to the other regimens[9].

The purpose of the study is to see the clinical response in biopsy proven lupus nephritis patients at the rheumatology department of Fauji Foundation Hospital, Rawalpindi by comparing MMF and CYC as induction therapy and determines the superiority of one over the other if any. Local data regarding the efficacy and superiority of one regimen over the other is sparse. This study will help clinicians to get an idea of the response of both treatments in our population.

MATERIAL AND METHODS

Approval was taken from the institutional ethical review board. Patients were selected by non-probability consecutive sampling. As this was a retrospective study without any investigation or intervention done besides those for clinical case management by the treating rheumatologists, written informed consent was not required. This was a retrospective, randomized study on patients with biopsy proven LN which are on follow-up from July 2016 to December 2017 at the Department of Rheumatology, Fauji Foundation Hospital, Rawalpindi, Pakistan. Inclusion criteria for the study was SLE patients with renal biopsies showing features consistent with LN Class III, IV, or Class V. Patients with non-proliferative lesions, i.e., Class I, II and those with Class VI LN were excluded. A total of 28 patients (only females) of ages between 18 to 50 all ages were included in this study. The primary endpoint was to study the response to therapy, i.e., complete response (CR). The secondary endpoint was a partial response (PR). The duration of the study was 1.5 years. All patients were diagnosed according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification by light microscopy and immunofluorescence analysis.[12]

Patients were divided into 2 groups. MMF Group includes 14 patients and was given induction with 2.5 gram per day MMF for 24 weeks and CYC Group includes 14 patients and was given cyclophosphamide according to NIH protocol for 24 weeks. Along with CYC dose, 1-gram methylprednisolone was also given with each CYC pulse. Adjunct therapy includes prednisolone (0.5-1 gram/kg) in tapering doses, Hydroxychloroquine (HCQ) (6.5 mg/kg), and angiotensin converting enzyme inhibitor (ACE) or aldosterone receptor antagonist (ARB) in a stable dose.

Information was collected from the hospital records at baseline at the time of renal biopsy before induction therapy and subsequently at 24 weeks. Baseline characteristics include age, ANA, AntiDsdna, haemoglobin, white Blood cell count (WBC), platelets count, urea, creatinine, erythrocyte sedimentation rate (ESR), serum alanine aminotransferase (ALT), serum albumin, complement levels, systemic lupus erythromatosis disease activity index (SLEDAI), stages of LN and 24-hour urinary protein in grams.

The renal response was seen in 2 treatment groups. Complete response (CR) is defined as a decrease in proteinuria to less than 0.5 gram/24 hours at the end of induction therapy. Partial response (PR) is defined as, i.e., a decrease in proteinuria less than 50% of the baseline value at 24 weeks. Treatment failure was defined as urinary protein excretion that remained at/or >3.0 g/24 hour or increase in proteinuria at the end of 24 weeks of therapy. PR, CR, and treatment failure was seen in both treatment groups.

Data was analysed using SPSS version 23.0. For baseline characteristics like age, haemoglobin, WBC, platelets, urea, creatinine, ESR, ALT, Albumin, and 24-hour urinary proteins results are given as mean±standard deviation (SD) and to compare the baseline characteristics and renal responses between the two treatment groups paired T test was used. The level P <0.05 was considered as the cut-off value for significance.

RESULTS

The results of the study are shown in the tables.

Table-1: Characteristics of MMF group and CYC group at baseline and at 24 weeks

Characteristics	Baseline values (MMF group) n=14	Baseline values (CYC group) n=14	*p*-value	24 weeks values (MMF Group) n=14	24 weeks values (CYC Group) n=14	*p*-value
Mean age (years)±SD	27.64±10.86	32.42±9.82	0.241	27.64±10.86	32.42±9.82	0.241
Duration of disease -mean±SD(months)	38.78±20.86	60.00±29.80	**0.048**	38.78±20.86	60±29.80	**0.048**
Mean haemoglobin (mg/dl)±SD	9.67±2.20	10.54±2.02	0.188	11.10±1.02	11.15±2.10	0.930
Mean leukocyte count($\times10^3$cells)±SD	6.68±2.38	6.36±2.12	0.713	7.83±2.68	7.79±3.43	0.979
Mean platelet count ($\times10^3$cells)±SD	231.14±96.09	232.00±66.88	0.979	289.35±82.35	249.64±81.83	0.250
Mean urea (mg/dL)±SD	6.98±2.48	4.72±1.04	**0.015**	5.51±1.13	5.07±1.03	0.293
Mean serum creatinine (mmol/L)±SD	97.57±40.37	80.47±24.33	0.159	82.35±11.20	77.21±6.91	0.164
Mean serum Albumin(mg/dL)±SD	36.64±3.17	37.28±4.49	0.630	36.07±3.68	37.07±3.31	0.330
Mean ESR (mmHg in first hour) ±SD	35.14±11.88	27.00±7.85	0.075	28.28±15.64	26.50±4.07	0.698
Mean serum ALT (IU/L) ±SD	38.07±23.74	36.42±12.95	0.851	31.21±11.00	40.35±14.79	0.80
Mean proteinuria (gram/24 hours)	2.63±1.27	2.36±0.87	0.472	0.75±0.57	0.98±0.60	0.284
C3(units)g/L	0.80±0.232	0.72±0.331	0.474			
C4(units) g/L	0.248±0.194	0.252±0.173	0.962			
SLEDAI (disease activity index)	No flare-0 Mild or moderate-8 Severe-6	No flare-0 Mild or moderate flare-11 Severe flare-4	-------	No flare-7 Mild or moderate- 7 Severe-0	No flare-8 Mild or moderate flare-5 Severe flare-1	--------
ANA by Immunofluorescence	Positive-12 Negative-2	Positive-12 Negative-2	-------			
AntiDsdna	Positive-8 Negative-6	Positive-8 Negative-6	-------			

Table-2: Stages of LN and 24-hour urinary protein of MMF group and CYC group at baseline and after 24 weeks of induction therapy

MMF group serial no.	Renal biopsy stage	24-hour urinary protein (gms/24 hour) at baseline	24-hour urinary protein (grams/24 hour) at baseline	CYC group serial no.	Renal biopsy stage	24-hour urinary protein (grams/24 hour) at baseline	24-hour urinary protein (grams/24 hour) at baseline
1.	V	1.69	1.54	1.	IV	2.28	0.98
2.	IV	4.48	0.45	2.	V	1.00	0.22
3.	III	3.10	0.21	3.	IV	1.84	0.43
4.	IV	1.55	1.80	4.	IV	2.90	0.84
5.	V	3.88	0.72	5.	III	2.50	2.16
6.	III	5.90	0.92	6.	III	3.40	0.91
7.	IV	3.20	0.20	7.	V	2.12	2.68
8.	V	1.80	1.71	8.	IV	2.60	1.68
9.	V	2.75	0.70	9.	IV	1.96	0.50
10.	III	1.90	0.10	10.	III	2.84	0.97
11.	III	3.20	0.38	11.	III	2.30	1.10
12.	IV	1.40	0.69	12.	IV	4.40	1.20
13.	IV	2.90	1.00	13.	V	1.80	0.32
14.	III	1.10	0.16	14.	III	1.20	0.45

Table-3: Renal responses in MMF group and CYC group and its relationship with renal biopsy stage

	MMF group	CYC group	*p*-value
Complete response (CR)	6 (42.85%)	5 (35.71%)	0.470
Partial response (PR)	5 (35.71%)	6 (42.85%)	0.132
Treatment failure	3 (21.42%)	3 (21.42%)	0.212
Stage 3 (PR or CR) n=5	5 (100%)	4 (80%)	0.150
Stage 4 (PR or CR) n=6	4 (80%)	5 (83.33%)	0.393
Stage 5 (PR or CR) n=3	2 (50%)	2 (66.66%)	0.086
Overall response in each group either complete or partial	11 (78.57%)	11 (78.57%)	0.000

No relationship was found between the mean age, haemoglobin, WBC, platelets, creatinine, proteinuria in both MMF group and CYC group at baseline and at 24 weeks. *p*-value >0.05. Mean urea and mean duration of disease was found to be statistically significant in both groups. *p*-value <0.05.

As shown in the tables the difference in the cumulative probability of complete and partial response was not statistically significant between the two groups (p=0.470 for CR) and (p-value 0.132 for PR). The cumulative probability of the overall response was also not statistically significantly different between the two groups.

DISCUSSION

Systemic lupus erythromatosis is a chronic disease with high morbidity and mortality and LN has an even graver prognosis if not treated early and on time. Treatment of LN is an entity that has not been studied in Pakistan.

This is a retrospective, randomized, open-label comparative study of the efficacy of IV CYC compared to oral MMF in the induction therapy of LN in Pakistani patients. There is a paucity of data on this subject in our patients. The majority of studies have reported on Caucasians, Afro-Americans and Chinese. Considering the large population of our country this study and further large scale multicentric study are essential.

In our studies, we tried to do a retrospective analysis of the treatment we have given in the last one and a half years in our department, about the efficacy of both of these regimens which are most of the time used in our hospital as a first line induction therapy. In our department of rheumatology at Fauji Foundation Hospital, we mostly used MMF for younger patients due to better safety concerns and lesser risk of infertility while those patients above 40 years of age with their families completed are given NIH regimen.

In our study, about 6 (42.85%) patients in MMF group showed complete response and 5 (35.71%) patients showed partial response. And treatment failure is seen with 3 (21.42%) patients. Most of the response is seen in patients having stage III LN 5 (100%), 4(80%) in stage IV, and 2 (50%) in stage V.

In the second group in CYC group, complete response was achieved in 5 (35.71%) patients and 6 (42.85%) showed partial response. And treatment failure is seen with 3 (21.42%) patients. Most of the response is seen in patients having stage IV 5(83.33%), 4 (80%) in stage III, and 2 (66.6%) in stage V.

This gives us a total response rate (CR+PR) of 78.57% in the MMF group and 78.57% in the CYC group. There is always a debate going on that when to use NIH regimen or MMF for LN. The data showed that both therapies are equal in efficacy.[13] In stage 5 LN there is evidence that MMF may be superior to the NIH regimen.[9] In a multinational, two phase study by Appel GB and colleagues MMF group showed 56% response rate and CYC shows 53% response which is lesser than achieved in our study.[10]

In a study conducted by M. Sahay and colleagues with a sample size of 56 patients in the CYC group the response rate was 71.4% and CR is achieved in 53.5% of patients and MMF group with 48 patients was 72.9 % and CR was achieved in 52% of the patients. These results are comparable to our study but fewer patients achieved complete remission in our study as compared to this study.[11]

In another study comparing NIH, MMF and rituximab by Goshwami RP and colleagues with a large sample size showed the renal response of 90.3%, 90.9% and 72% with NIH regimen, MMF and Rituximab.[13] In a small study of 40 patients by Mendonca and colleagues Of the 40 patients, 17 were randomized to the MMF group and 23 to the CYC group. Complete remission was seen in 9(52.94%) patients in the MMF group and 11 (47.82%) in the IV CYC group. Partial remission was seen in 6 (35.30%) in the MMF group and 9 (39.13%) in the IV CYC group.[14]

Our study highlights that our population have a very good response to MMF or CYC during the induction therapy of LN with comparable results. However, Pakistan is a underdeveloped country with the majority of the population in the lower socioeconomic status, the cost of MMF is a limiting factor in its use in routine clinical settings. Our centre is government funded with free availability of MMF, despite which there were several episodes of poor compliance among the patients. This factor also accounts for the compliance fatigue in these patients compounded with the high cost of therapy with MMF. In the case of CYC it is a monthly dose and is cost-effective and hence compliance rates may be better. This aspect requires further study and was not within the scope of this study.

There are no local studies regarding the comparison of MMF and CYC in our Pakistani population. The study prompts an urgent and essential need of a multicentric large population study comparing the response of these two drugs in the management of LN. So that management of the local rheumatologists and nephrologists about the treatment of LN will be improved.

Our study had certain limitations which include non-probability sampling technique, no male SLE patients, one center study, and a small sample size. Cost of MMF for treatment is also a limitation and CYC is much cheaper than MMF. SLE nephritis patients with biopsy proven nephritis were few as patients don't give consent for renal biopsy and in many cases, treatment is started without renal biopsy this gives few patients with biopsy proven nephritis.

The study could have been done as multicentre study which could have increased the sample size as well as a variety of patients. Another limitation is that most of the patients in the sample have proteinuria but renal function tests are normal when the induction therapies are given so

improvement in renal functions as a response to therapy cannot be assessed.

CONCLUSION

The present study concludes that MMF is as good as CYC in the induction therapy of mild-to-moderate LN in Pakistani patients.

Conflict of interest:

This study has no conflict of interest to declare by any of the authors.

AUTHORS' CONTRIBUTION

HG, MSM, SS: Data collection, data analysis, data interpretation, write-up. BS, AN: Conceptualization of study design, proofreading. MK: Literature search.

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Address for Correspondence:
Muhammad Salman Mushtaq, Department of Rheumatology, Fauji Foundation Hospital Rawalpindi-Pakistan
Cell: +92 333 547 9735
Email: salmanmushtaq@ymail.com