CLINICAL AND BIOCHEMICAL PREDICTORS OF RESPONSE TO MYCOPHENOLATE MOFETIL FOR INDUCTION TREATMENT OF PROLIFERATIVE LUPUS NEPHRITIS : COMPARED TO INTRAVENOUS CYCLOPHOSPHAMIDE

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Abstract

Background: The accepted standard of care for induction of lupus nephritis has been cyclophosphamide but recent trials suggest that mycophenolate mofetil may be more effective and less toxic. The objective of the study was to evaluate the patients achieving partial remission and complete remission after induction treatment of lupus nephritis by cyclophosphamide and mycophenolate mofetil.

Materials and methods: It was a quasi-experimental study performed in the Department of Nephrology of Chittagong Medical college Hospital (CMCH). A total of 100 patients of lupus nephritis (Class III and IV) who fulfilled the designated criteria were enrolled in this study by non-probability voluntary sampling method. The treatment was given on patient's choice. After screening and treatment initiation, patients were assessed at 12 and 24 weeks. All the data were compiled in a structured case record form. Results: In the present study 48 patients (53.3%) in mycophenolate mofetil group and 42 patients (46.7%) in intravenous cyclophosphamide group completed 24 weeks of induction treatment of lupus nephritis. As per protocol analysis, 25(58.083%) of 48 patients in the MMF group and 7(16.7%) of 42 patients in intravenous cyclophosphamide group achieved complete remission at 24 weeks.

Conclusion: Induction therapy with Mycophenolate mofetil was superior to intravenous cyclophosphamide in inducing complete emission of lupus nephritis in this study.

Key words: Lupus nephritis; Mycophenolate mofetil; Cyclophosphamide.

Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease with a prevalence that varies with the age, sex, and race, affecting young women, predominantly in fertile age, particularly of Afro-Caribbean origin.[1,2] The prevalence of kidney involvement at the time of diagnosis of SLE is 16%,reaching 39% during the evolution of the disease. Renal involvement in SLE is an important cause of morbidity and mortality.[3,4] The most common clinical sign of renal disease is proteinuria, but hematuria, hypertension, varying degrees of renal failure and active urine sediment with red blood cell casts can all be present.The World Health Organization (WHO) workshop in 1974 first outlined several distinct patterns of lupus-related glomerular injury, these were modified in 1982. In 2004 the International Society of Nephrology in conjunction with the Renal Pathology Society again updated the classification. Class I nephritis describes minimal mesangial deposits on immuno fluorescent or electron microscopy. Class II designates mesangial immune complexes with mesangial proliferation.The subject of lupus nephritis is presented under acute nephritic syndromes because of the aggressive and important proliferative lesions seen in class III–V renal disease. Hypertension, active urinary sediment, and proteinuria are common with nephrotic-range proteinuria in 25–33% of patients. Elevated serum creatinine is present in 25% of patients.The treatment of proliferative Lupus Nephritis (LN) can be staged as a period of intensive immuno suppressive therapy aimed at halting immunological injury (Induction therapy).[5] In a first induction phase an early remission should be achieved avoiding the chronicity of renal disease. Traditionally, the National Institutes of Health (NIH) regimen with intermittent Intravenous (IV) Cyclophosphamide (CYP) has been considered the standard of care for proliferative LN. This regimen involves the use of IV CYP dosages of 0.5-1 g/m^2 body surface area for 6 months. Initially, several randomized and controlled clinical trials of the NIH demonstrated that oral or IV CYP was an effective therapy for the treatment of severe LN.[6,7]

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Mycophenolate Mofetil (MMF) was introduced into use in renal transplant patients in the 1990s and was shown to have a favorable safety profile.The largest trials demonstrated that MMF was equivalent and possibly superior to IV CYP as induction therapy for severe LN, with a safer side-effect profile.[8] Therapy differs depending on the pathologic lesion. Focal or diffuse lupus nephritis (Class III-IV) confers a much greater risk of progression, potentially to ESRD and requires more aggressive treatment with immuno suppressive medications.[9] As treatment protocol of lupus nephritis long time course we have to choose appropriate regimen for the patient considering their socioeconomic status, their age, sex and disease severity.

The aim of the study was to evaluate patients achieving partial remission and complete remission after induction treatment of lupus nephritis by MMF or CYP on the basis of clinical and biochemical parameter.

Materials and methods

A quasi experimental study was done in the Department of Nephrology, Chittagong Medical College Hospital, Chattogram during the period of one year from January 2016 to December 2016. A total 100 patients were enrolled in the study newly diagnosed with lupus nephritis according to the American College of Rheumatology (ACR) revised criteria by persistant proteinuria >0. 5gm/day or greater than 3+ by dipstick and active urinary sediment(>5RBC/high power field, >5 white blood cell/ high power field or cellular cast including RBC and WBC casts, granular ,tubular and mixed casts) and kidney biopsy showing class III and class IV according to the International Society of Nephrology. Patients who were not treated with immuno suppressive agent previously excluding corticosteroid for lupus nephritis were included in the study. ESRD patient with lupus nephritis and lupus nephritis patient with pregnancy were excluded from the study.The treatment was given on patients choice. Each patient provided written consent before inclusion. Ethical approval was obtained from ethical committee, Chittagong Medical College Hospital. Among the 100 patients, 50 were assigned to MMF and 50 to IV CYP. After 24 weeks, 90 patients(48 patients in MMF group and 42 patients in IV CYP group) remained in the study.

Oral MMF was given twice daily, titrated from 0.5 g twice daily in week 1 and 1.0 g twice daily in week 2, to a target dosage of 1.5 g twice daily in week 3. IV CYP was given in monthly pulses of 0.5 to 1.0 g/m^2, according to the modified NIH protocol. Both groups received oral prednisone, with a defined taper from a maximum starting dosage of 60 mg/d. The induction phase was defined as 24 weeks response, because 24-wks response can predict disease outcome. The responses to induction therapy were defined by complete remission and partial remission. Complete remission was defined as urinary protein excretion 0.3 g/24 h with normal urinary sediment, normal serum albumin concentration, and improved or stable renal function. Partial remission was defined as stable or improved renal function with reduction of proteinuria by ≤ 50%, proteinuria within the range of 0.3 to 3 g/24 h and albumin ≥30 g/L.

Main variables included in study urine analysis, serum creatinine level, 24 hours urinary total protein, serum albumin. Standard laboratory assessment were performed locally at entry into the study & at 12 weeks & 24 weeks interval to assess the efficacy of the study drug. After screening and treatment initiation, patients were assessed at 12 and 24weeks. Data was collected by interview & laboratory investigation. All the data were compiled in a structured case record form.

All patients were examined at the Department of Nephrology CMCH. For urine analysis midstream specimen of urine was collected. A second midstream clean catch urine sample about >20 ml was taken and placed in a container by standard procedure.Urine samples were tested by multiple reagent strips and microscopic analysis. Reagent strips for convenient office or ward urinalysis were used for assessment of protein, blood, leukocytes. A 24 hour urine collection to measure protein was done by collecting urine in a special container over a full 24 hour period. The patient was instructed to collect all urine for a 24 hour period day before. The blood were collected by a trained lab technologist or researcher herself according to guidelines on drawing blood by World Health Organization (WHO). Blood sample were mixed with proper anticoagulant as per direction of the laboratory and were sent for analysis of estimation of different variables before starting of hemolysis

which might have some impact on the results. All relevant investigations were done in the biochemistry and Clinical Pathology Departments of CMCH or if needed in one or two renowned, modern laboratory of Chattogram. Cost were borne by the researcher herself.

Collected data were verified and edited for its consistency then compiled, tabulated and processed in the computer according to the key variables to find a master sheet. Stastical significances were done using appropriate tests of significance e.g continuous variable were compared through student's t –test, for the categorical variable the chi-square test were used by stastical software IBM SPSS version 20. A probability of <0.05 was considered statistically significant for all test. Finally, data were presented by chart, diagram, univariate and multivariate tables accordingly.

Results

A total of 100 patients with diagnosis of class III and class IV lupus nephritis selected for study were distributed into two groups -50 patients treated by MMF and 50 patients treated by CYP.In the present study 48 patients(53.3%) in MMF group and 42 patients (46.7%) in IV CYP group completed 24 weeks of induction treatment of lupus nephritis .

The mean age of the patients between two groups was 25.94 vs. 26.05. Sociodemographic profile among the patients were analyzed where about 94.4% patients were female. Regarding socioeconomic status among the study group, most of patients (71.4%) receiving IV CYP were from lower middle class. Most of the patients of MMF groups (68.8%) belonged to upper middle class.

After 24 weeks follow up, there was significant reduction of urine RBC in MMF group. In MMF group, only 6.3% patient had urine RBC >11-25/HPF. But in CYP group, urine RBC>11-25/HPF remained the same before treatment and after 24 weeks follow up (Table I).

Table I : Distribution of urine RBC(>11-25/HPF) among the study group (With χ^2 test significance).

STUDY GROUPS	Urine RBC/HPF			χ^2 Test Significance
	Initial* n (%)	12 weeks n(%)	24 weeks n(%)	
MMF	19 (39.5%)	9 (18.7%)	3 (6.3%)	χ^2 = 6.849 p=0.032
CYP	11 (26.1%)	11 (26.1%)	11 (26.1%).	

● S = Significant (p < 0.05), NS = Not Significant (p > 0.05). HS= Highly significant (p<0.01) * baseline values before induction

After 24 weeks of treatment no patient in MMF group had +++ albumin but number of patient in CYP group remained same as after 12 weeks of induction (Table II).

Table II : Distribution of urine albumin among the study groups at 24 weeks follow up (With χ^2 test significance).

STUDY GROUPS		Urine Albumin				χ^2 Test Significance
		Trace n (%)	+ n (%)	++ n (%)	+++ n (%)	
Follow up at 24 weeks	MMF	33 (68.8%)	10 (20.8%)	5 (10.4%)	0(0.0%)	χ^2 = 34.266 p = 0.000
	CYP	5 (11.9%)	15 (35.7%)	12 (28.6%)	10 (23.8%)	

● NS = Not Significant (p > 0.05), HS = Highly Significant (p < 0.01).

Around two third (80%) patients in MMF group had no urinary cast where only one third (42.9%) patients in CYP group had no urinary cast after 24 weeks of follow up (Table III).

Table III : Distribution of urine cast between the study groups (With χ^2 test significance).

STUDY GROUPS		Urine cast		χ^2 Test Significance
		Nil n (%)	Present n (%)	
Follow up at 24 weeks	MMF	34 (70.8%)	14 (29.2%)	χ^2 = 7.186 p = 0.007
	CYP	18 (42.9%)	24 (57.1%)	

HS = Highly Significant (p < 0.01).

The number patients having .0.5-3gm/day of urine protein was more in IV CYP group than MMF group after 24 weeks of induction treatment (Table IV).

Table IV : Distribution of 24 hours urinary total protein(>0.5-3 gm/day) between the study group (With χ^2– test significance).

STUDY GROUPS	24 hours UTP(gm/day) (>0.5-3gm/day)			χ^2 Test Significance
	Initial* N (%)	12 weeks n (%)	24 weeks n (%)	
MMF	44 (91.66%)	31 (64.58%)	23 (47.91%)	χ^2 = 3.9054 p=0.1418
CYP	36 (85.71%)	25 (59.52%)	35 (83.33%)	

NS = Not Significant (p > 0.05),* Baseline values before induction.

Serum creatinine levels in all patients who had slightly increased serum creatinine at the start point returned to normal at the last follow up in two groups (p=0.4894). At 24 weeks follow up the difference between the MMF and IV CYP group with respect to level of serum albumin was not significant (p=0.8189). The reduction of value of anti double stranded DNA was higher in MMF group than IV CYP group after the last follow up but it was not statistically significant (p=0.4999).

As per protocal analysis,25(58.083%) of 48 patients in the MMF group and 7(16.7%) of 42 patients in IV CYP group achieved complete remission at 24 weeks (Table V). Patients under MMF group were three times more likely to enter complete remission compared with those treated with IV CYP group. Partial remission occurred in 23(47.91%) patients in MMF group and 35 (83.3%) in IV CYP group.

Table V : Distribution of outcome of induction treatment of lupus nephritis between the study groups after 24 weeks (With χ^2 test significance).

Outcome	Study Groups		χ^2 Test
	MMF n (%)	CYP n (%)	Significance
Complete Remission	25(58.083%)	7(16.7%)	χ^2= 12.2623 p = 0.000462
Partial Remission	23(47.91%)	35(83.3)	
Total	48	42	

HS = Highly Significant ($p < 0.01$).

Discussion

The study was attempted to make a comparative clinical outcome of MMF and IVCYP in the treatment of lupus nephritis. After 24 weeks ,90 patients (48 patients in MMF group and 42 patients in IV CYP group) remained in the study.Two patients in MMF group and 8 patients in IV CYP group failed to complete 24 weeks induction phase.Among the eight patients who failed to complete 24 weeks treatment in IV CYP group were due to death, adverse events and loss to follow up. There were. two deaths in IV CYP group during treatment. One patient died due to SLE within a week of receiving the first dose of IV CYP. The other patient received two doses and death occurred after 8 weeks later due to active lupus. Two patients in MMF group were lost to follow up.

The mean age of the both study group was 25.99. About 94.4% patient in the study were female. Regarding socioeconomic status among the study group, most of patients receiving IV CYP were from lower middle class (71.4%). Most of the patients of MMF groups belonged to upper middle class (68.8%). In our study age and sex of both groups were closely matched so that their effects were minimized on expected results. In our study drug response were counted by observing 24 hours urinary protein, urinalysis, serum creatinine level, serum albumin level during study period.

Initially, several randomized and controlled clinical trials of the NIH demonstrated that oral or IV CYP was an effective therapy for the treatment of severe LN.[10] In the studies of NIH it was demonstrated that IV administration had better long term effectiveness. In NIH and ELNT trial it was demonstrated that renal flares were frequent, even in those patients who had a complete response to CYP.[11] Although several uncontrolled studies had suggested the safety and efficacy of MMF in lupus nephritis.

Sedhain A et al twenty-four-hour urinary protein (gm/1.73m^2) reduced from 4.47 to 0.94 in CYC and from 4.5 to 0.62 in the MMF group.[12] Primary end point was achieved in higher percentage of patients with MMF than CYC (28.6% vs. 19%) which were consistent with our study.The number patients having 0.5-3gm/day of urine protein after 24 weeks was more in IV CYP group than MMF group (MMF 47.91% vs. CYP 83.33%).

Ong et al compared MMF versus IV CYP as induction therapy for proliferative lupus nephritis.[13] The MMF group had less proteinuria compared with IV CYP. In our study it was observed that urinary albumin was significantly higher with CYP after24 weeks follow up.The number patients in CYP group having +++ albumin was 10 fold greater than MMF group which was highly significant (Table II).

We found that urine protein, serum albumin, urine RBC and urine RBC cast all improved during treatment by MMF and IV CYP.Urine RBC and urine RBC casts are valuable marker to assess drug response. In our study after 24 weeks follow up,only 6.3% patients in MMF group had urine RBC >11-25/HPF,but in IV CYP group number of patients having urine RBC >11-25/HPF remained

same after 24 weeks follow up (Table I).Our findings were consistent with previous study.[13-15]

Chan et al randomized 42 patients with diffuse proliferative lupus nephritis to be treated with prednisolone and MMF for 6months or prednisolone and CYP for 6 months.[14] The improvement in the serum albumin and creatinine concentrations were similar in both groups which was similar with our study. In the present study it was observed that number of patients having urinary proteins was significantly higher in IV CYP group after 24 weeks follow up.

Ginzler et al randomized 140 patients with severe LN and an average serum creatinine of 1.1 mg/dl to receive oral MMF (Mean dose 2.7 gm/d) or NIH-dose IV CYP as induction therapy for 24 weeks.[15] In their study showed the superiority of MMF over IV CYP. A significantly higher percentage of patients in the MMF group reached the primary end point (Complete remission) compared with IV CYP at 24 weeks (22% versus 6%). In our study complete remission achieved by MMF was three times greater than IV CYP (58.083% vs.16.7% p=0.000462). Partial remission occurred in 23(47.91%) patients in MMF group and 35 (83.3%) in IV CYP group.

Appel et al then conducted an open-label trial that randomized 370 patients with severe LN and an average serum creatinine of 1.1 mg/dl to receive prednisone plus either MMF (Average dose 2.6 gm/d) or NIH-protocol IV CYP for 24 weeks as induction therapy.[16] The response to treatment at the end of induction therapy was similar in the MMF and IV CYP groups, with 56% and 53% of patients responding to treatment. But in our study MMF showed superiority over IV CYP.

Limitation

The study was for short duration and single centered.There was relative small sample size for class III and class IV lupus nephritis patients.Due to lack of funding and time constraint rebiopsy could not be done.

Conclusion

Induction therapy with mycophenolatemofetil was superior to intravenous cyclophosphamide in inducing complete remission of lupus nephritis in this study. Complete remission achieved by mycophenolate mofetil was three times greater than intravenous cyclophosphamide which was statistically significant.

Recommendation

Large scale multicenter study should be done to get the national scenario.Study involving long duration follow up with cohort fashion should be done to explore more practical information.

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Contribution of authors

RBK-Conception, design, acquisition of data, drafting & final approval.
PKD-Interpretation of data, critical revision & final approval.
MNH-Data analysis, critical revision & final approval.
MA-Acquisition of data, data analysis, drafting & final approval.

Disclosure

All the authors declared no competing interest.

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