Chattagram Maa-O-Shishu Hospital Medical College Journal
Volume 22, Issue 1, January 2023

Original Article

Risk Assessment of Cyclophosphamide and Mycophenolate Mofetil after Induction Treatment of Lupus Nephritis: A Single Center Quasi-Experimental Study

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Abstract

Background: *The comparative safety of immunosuppressive drugs such as cyclophosphamide and mycophenolate mofetil for patients with lupus nephritis remains controversial. The study aimed to investigate the specific side effects of cyclophosphamide and mycophenolate mofetil in lupus nephritis patient after induction treatment.*

Materials and methods: *It was a quasi-experimental study performed in the Department of Nephrology of Chittagong Medical College Hospital. A total of 100 patients of lupus nephritis 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. Infections were common in both treatment groups but significantly higher with intravenous cyclophosphamide group ((33.3% vs. 8.3%). Upper gastrointestinal syndrome occurred with 20(41%) patients in mycophenolate mofetil group and 7(16.7%) patients in intravenous cyclophosphamide group (RR=5.8333). Regarding other adverse effect, 10 patients of intravenous cyclophosphamide and two patients of mycophenolate mofetil group had amenorrhea (23.8% vs.4.2%). Alopecia (11.9%) was seen only by intravenous cyclophosphamide group ((RR=0.0798).*

Conclusion: *Induction therapy with Mycophenolate mofetil was superior to intravenous cyclophosphamide in lupus nephritis in this study. Mycophenolate mofetil appeared to be better tolerated than cyclophosphamide.*

Key words: Cyclophosphamide; Lupus nephritis; Mycophenolate mofetil.

INTRODUCTION

SLE is known as an autoimmune disease with complex pathogenic mechanisms that always lead to multisystem damage; the long duration of use of immunosuppressive drugs and glucocorticoids increases the risk of premature death.[1-3] 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.[4-5] During the treatment, nearly all patients report one or more Adverse Events (AEs), and these AEs shape doctors' preferences, especially when two drugs are considered to be equivalent. Serious AEs (SAEs) refer to events that result in death, are life threatening, require inpatient hospitalizationor cause prolongation of existing hospitalization result in persistent or significant disability/ incapacity, lead to a congenital anomaly/ birth defect or that require intervention to prevent permanent impairment or damage.These effects can directly demonstrate the safety of available drugs in different aspects, eliminating the interference of more

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Date of Submission : 08.11.2022
Date of Acceptance : 05.12.2022

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mild AEs. However, mainly because of an absence of head-to-head trials and SAE data, the comparative safety is largely unknown.[6] Lupus Nephritis (LN) is a common and severe manifestation of Systemic Lupus Erythematosus (SLE) that can lead to ESRD and death in our country. SLE particularly affects women during their fertile age. Most of the lupus nephritis patient of our country are socioeconomically disadvantaged. Individual with lower socioeconomic status have been shown to have incidence, severity and mortality from lupus than those to higher economic status. Significant predictors of poor outcomes and disease progression have included poverty, lack of education, lack of support and poor compliance of patient.

Therapy for lupus nephritis should aim at symptomatic control, preservationof renal function, reduction of renal flares, prevention of treatment related complication and ultimately reduction in mortality.

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 efficacy, tolerability, safety of Mycophenolate Mofetil (MMF) and Cyclophosphamide (CYP) should consider on choosing the appropriate regimen for the patients. So proposed study designed to find out the efficacy, safety, patient compliance to MMF and CYP on induction treatment of lupus nephritis would be useful for lupus nephritis patient of our country. Mycophenolate Mofetil (MMF) is a powerful immunosuppressant that exerts a reversible inhibition of inosine monophosphate dehydrogenase, the rate limiting step in de novo purine synthesis, which is essential for lymphocyte proliferation.Initially, its use in LN was reserved for patients who had not responded to corticosteroid and CYP or had presented an unacceptable toxicity. Although several uncontrolled studies had suggested the safety and efficacy of MMF in lupus nephritis.[7-13]As CYP and MMF are shown to be equivalent as induction therapies for the treatment of LN, it is important to consider the respective severity and relative frequency of their acute/ subacute and chronic toxicities. Effective but very toxic therapy is common in autoimmune disease. In the last decade, clinical trials have shown that less toxic drugs are as effective for treating lupus nephritis.[14] With respect to the induction treatment of LN, a number of systematic reviews and meta analyses have been performed. One of the earliest of these analyses included four studies with a total of 268 patients, which found that leukopenia and amenorrhea were more common with CYP than with MMF treatment.[15] Similarly, another analysis of three studies (206 patients) found a statistically lower incidence of leukopenia in the MMF treatment group.[16] In a meta-analysis and meta regression comparing CYP and MMF in 10 studies (847 patients as induction and/or maintenance therapy for LN) there was a significantly lower risk of developing amenorrhea and leukopenia with MMF.[17]

On different literature reviews show that MMF showed equivalency to CYP for induction treatment of lupus nephritis. LN is most commonly seen in premenopausal women, some adverse effects of CYP (Alopecia and amenorrhea) are especially troubling in this patient group.Whereas short- or long-term therapy with MMF (For LN or in transplantation, respectively) is not associated with ovarian failure, shortcourse (6 months) or long-course (2 years) intermittent monthly /quarterly pulse CYP therapy is associated with a cumulative dose/duration-dependent amenorrhea (incidence reported to be 23–56%) which may be permanent.[18-20] Even if amenorrhea does not occur with CYP, premature menopause may occur years after treatment. The use of CYP is also associated with a risk of developing hemorrhagic cystitis and/or transitional cell carcinoma of the bladder. MMF has not been associated with either of them in any of the controlled trials using this agent.[3]

In the present study, the efficacy, safety and tolerability of oral mycophenolate mofetil plus corticosteroids were compared with those of IV CYP plus corticosteroid for inducing remission of active lupus nephritis.

MATERIALS AND METHODS

A quasi experimental study was done in the Department of Nephrology, Chittagong Medical College and hospital, Chattogram during the period of one year from January 2018 to December 2018. 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 persistent proteinuria >0.5 gm/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 immunosuppressive 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. 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.Each patient provided written consent before inclusion. Ethical approval was obtained from Ethical Review Committee, Chittagong Medical College Hospital.

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. Standard

Laboratory assessment were performed locally at entry into the study and at 12 weeks and 24 weeks interval to assess the efficacy and toxicity of the study drug. After screening and treatment initiation, patients were assessed at 12 and 24 weeks. Data was collected by interview and laboratory investigation. 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.Statistical 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. Risk analysis was done by relative risk and Number Needed to Treat (NNT) and Number Needed to Harm (NNH). Statistical software IBM SPSS version 20 was used for all the analysis. 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 intotwo 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.

Table I Summary of reasons for premature withdrawal from treatment

Parameter	MMF Group(n=50)	CYP Group (n=50)
Complete 24 weeks induction	48	42
Phase		
Reasons for withdrawl		
Adverse events	0	2
Loss to follow up	1	1
Patient died	0	2
Noncompliance	1	3

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. One patient in MMF group was lost to follow up.

Table II Distribution of adverse events (Reported by patients who completed 24 weeks induction treatment) among the study groups (With χ^2 test significance)

Adverse Events	STUDY GROUPS				χ^2 Test Significance
	MMF		CYC		
	n	%	n	%	
Infections Present	4	8.3	14	33.3	$\chi^2 = 8.750$
Absent	44	91.7	28	66.7	$p = 0.003^{HS}$
Gastro-intestinal symptoms Present	20	41.6	3	7.14	$\chi^2 = 5.034$
Absent	28	58.3	39	92.8	$p = 0.0024^{HS}$
Menstrual Irregularities Present	2	4.2	10	23.8	$\chi^2 = 7.479$
Absent	46	95.8	32	76.2	$p = 0.006^{HS}$
=Alopecia Present	0	0.0	5	11.9	$\chi^2 = 6.050$
Absent	48	100.0	37	88.1	$p = 0.014^{S}$

* HS = Highly Significant ($p < 0.01$), NS = Not Significant ($p > 0.05$), S = Significant ($p < 0.05$).

Infections were common in both treatment groups but significantly higher with IV CYP group (14% vs. 4%, p=0.003). There were two with drawals in IV CYP group due to herpes simplex infection. Gastrointestinal symptoms (Nausea, vomiting, diarrhea) occurred more with MMF group than IV CYP group (41.66% vs.16.7% p=0.002). Regarding other adverse effects (23.8%) of IV CYP and 4.2% of MMF group had amenorrhea (p=0.006). Alopecia (11.9%) was seen only by IV CYP group.

Table IIIa Univariate analysis of risk measurement for MMF versus CYP groups

Treatment	Infection		RELATIVE RISK (RR) (95% confidence Interval)	p-value	NNH/NNT
	Present (n)	Absent (n)			
MMF	4	44	0.25 (0.0891-0.7011)	0.0084	4.000
CYP	14	28			

HS = Highly Significant ($p < 0.01$), NNH=Number Needed to Harm, NNT=Number Needed to Treat.

Risk of infection was lower in MMF group than IV CYP group (RR =0.25). If 4 patients treated by MMF and 4 patients treated by IV CYP, one less infection would be observed in MMF treatment (Table IIIa).

Table IIIb Univariate analysis of risk measurement for MMF versus CYP groups

Treatment	Gastrointestinal symptom		RELATIVE RISK(RR) (95% confidence Interval)	p-value	NNH/ NNT
	Present (n)	Absent (n)			
MMF	20	28	5.8333 (1.8644-18.2516)	0.0024	- 3.000
CYP	3	39			

HS = Highly Significant (p < 0.01), NNH=Number Needed to Harm, NNT=Number Needed to Treat.
MMF was harmful than IV CYP regarding gastrointestinal symptoms (RR=5.8333). If 3 patients were treated by MMF and 3 patients treated by IV CYP one more gastrointestinal symptoms would be observed in MMF treatment (IIIb).

Table IIIc Univariate analysis of risk measurement for MMF versus CYP groups

Treatment	Menstrual Irregularities		RELATIVE RISK (RR) (95% confidence Interval)	p-value	NNH/ NNT
	Present (n)	Absent (n)			
MMF	2	46	0.175 (0.0406-0.7540)	0.0193	5.091
CYP	10	32			

S = Significant (p < 0.05) NNH=Number Needed to Harm.
MMF was beneficial regarding menstrual irregularities. If 5 patients were treated by MMF and 5 patients treated by IV CYP, one less menstrual irregularities would be observed in MMF treatment (IIIc).

Table IIId Univariate analysis of risk measurement for MMF versus CYP groups

Treatment	Alopecia Present (n)	Absent (n)	RELATIVE RISK(RR) (95% confidence Interval)	p-value	NNH/ NNT
MMF	0	48	0.0798 (4.631-51.3)	0.043	8.496
CYP	5	37			

S = Significant (p < 0.05) NNH-Number Needed to Harm, NNT=Number Needed to Treat.
Risk of alopecia was observed only by IV CYP(RR=0.0798). If 8 patients were treated by MMF and 8 patients were treated by IV CYP, one less alopecia would be observed by MMF treatment (IIId).

DISCUSSION

A total of 100 patients were assigned (50 patients received MMF and 50 patients received Intravenous CYP). The treatment was given on patients' choice. Among the 100 patients, 50 was assigned to MMF and 50 to IV CYP. After 24 weeks, 90 patients 9(48 patients in MMF group and 42 patients in IV CYP group) remained in the study.The overall adverse events profiles of both MMF and IV CYP in our study (Table III) were consistent with previous studies. In our study univariate analysis of risk measurement regarding adverse events after 6 months of induction.

In a study of C Burchardi and D Schlondarff the mycophenolate group had fewer deaths and severe infections than the cyclophosphamide group (0 vs 2 and 1 vs 6, respectively).[21] In Chan et al study showed that infection was higher in cyclophosphamide group than MMF group {4 vs10 ,95% CI,19(5-42)}.[22] In our study serious infections were less common with MMF (4 vs14, RR=0.25, 95% CI,0.0891-0.7011, NNT = 4.000). Significantly, fewer MMF treated patients developed infections that required antibiotic treatment or hospitalization.In our study itwas highly significant that only 4 patients in MMF group developed infections than 8 patients in CYP group (33.3% vs. 8.3% p=0.003). Treatment discontinuation due to adverseevents was responsible for 2 study withdrawals in CYP group due to herpes simplex infection.
In C Burchardi and D Schlondarff, MMF group had morecases of diarrhea (15 vs 2) which was consistent with our study.[21] In our study, upper gastrointestinal symptoms were commonin MMF group which were self-limited (20 vs. 3, p <0.002, RR=5.8333, NNH = -3.000). In Chan et al in Ong et al, in Ginzler et al occurrence of amenorrhea was more in CYP group (0 vs 3, 0 vs 1,0 vs 2 respectively).[22-24] In our study 8 patients in IV CYP group and 2 patients in MMF group had amenorrhea (RR=0.175, p=0.0193, NNT=5.091).
In view of above discussion,MMF was associated with fewer side effects than induction treatment with IV CYP.

LIMITATION

Like any other scientific study, the present study has some limitations which deserve mention.The study was concluded with • Small sample size • Single centre study • Short term follow up.

CONCLUSION

Mycophenolate mofetil appeared to be better tolerated than intravenous cyclophosphamide. Upper gastrointestinal symptoms were common in group mycophenolate mofetil which were self limited but infection rate was higher with intravenous cyclophosphamide group.
So, regarding risk and benefit, mycophenolate mofetil is better than cyclophosphamide in our study though to conclude it large scale multicenter study should be done to get the national scenario.

RECOMMENDATION

Further studies should be carried out involving large number of participants in multiple centres to get the national scenario. Study involving long duration follow up with cohort fashion might explore more practical information.

ACKNOWLEDGEMENT

Grateful to the patients and by working hospital.

DISCLOSURE

The author declared no competing interests.

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