Original Article

TO COMPARE THE EFFICACY OF MYCOPHENOLATEMOFETYL WITH CYCLOPHOSPHAMIDE IN THE MANAGEMENT OF LUPUS NEPHRITIS

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ABSTRACT:

OBJECTIVE:

To compare the efficacy of mycophenolatemofetyl with cyclophosphamide in the management of lupus nephritis in local population and compairing the results with studies within aand out of Pakistan.

STUDY DESIGN:

Comparative study

SETTING:

All the cases admitted through OPD and emergency in Medical Unit IV of DHQ Hospital Faisalabad.

DURATION WITH DATES:

From 15-06-2011 to 14-02-2012.

SUBJECTS AND METHODS:

Seventy two patients meeting the inclusion criteria were included in this study. They were allocated randomly in two groups of 36 patients. Group A, received mycophenolatemofetyl(MMF)orally and group B received intravenous cyclophosphamide(CYC) as monthly pulses of 0.5 g/m^2 body surface area. Both groups received prednisolone at a dose of 1mg/kg/day with tapering by 10-20% at one week or two week intervals on the basis of clinical improvement Chi Square test was used to compare the efficacy of two drugs based on remission after 24 weeks. P value of $\leq$0.05 was taken as significant.

RESULTS:

The mean age of the patients in group A was 27.6±5.0 years and in group B was 28.4±4.9 years. In group A, there were 3 (8.3%) male patients and 33 (91.7%) female patients. In group B, there were 36 (100%) female patients. In group A, 9 (25%) patients got remission from the treatment and in group B, 2 (5.6%) patients got remission from the treatment.

CONCLUSION:

It is concluded from this study that mycophenolatemofetyl(MMF)administered orally is superior in efficacy to intravenous cyclophosphamide(CYC) in the management of lupus nephritis.

KEY WORDS: Lupus nephritis, efficacy, mycophenolatemofetyl(MMF), cyclophosphamide(CYC).

INTRODUCTION:

Systemic lupus erythematosus (SLE) is an inflammatory, multisystem disorder with arthralgia and rashes as the most common clinical features and cerebral and renal disease as the most serious problems. Lupus nephirtis is one of the most frequent visceral forms of Systemic lupus erythematosus and occurs in 50 – 80% of the cases.[2]Prevalence

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of lupus nephritis in population of Pakistan is an intermediate between Caucasians and other Asians.[3] WHO classifies the renal glomerular lesions in lupus nephritis into type I (normal), type II (mesangial proliferative), type III (focal and segmental Proliferative) type IV (Diffuse proliferative), type V (Membranous Nephropathy). [4] Treatment is not indicated for Type I andType II, as these histologic patterns portend an excellent prognosis as 100% & 90% 5year survival rates, respectively.[5] Cyclophosphamide is used as a monthly Intravenous bolus has been the standard of care for treating severe lupus glomerulonephritis (Type, III, IV, V) in past and currently, however, failure to achieve remission, is reported in 18 – 57% of patients who received cyclophosphamide.[6] Recent trial of 24 weeks has found Mycophenolatemofetyl to be more effective than intravenous Cyclophosphamide in inducing remission which showed 16 of 71 patients (22.5%) receiving Mycophenolatemofetyl and 4 of 69 patients (5.8%) receiving Cyclophosphamide had complete remission.[7] Another trial reveals that end-point of death or chronic renal failure and the rate of relapse free survival to be significantly higher with Mycophenolatemofetyl than with Cyclophosphamide.[8] Keeping in mind recent studies we carried out a study at DHQ Hospital to compare the efficacy of Mycophenolatemofetyl with Cyclophosphamide in the management of lupus nephritis.

MATERIALS & METHODS:

Study design: comparative study

Setting: All the cases admitted through OPD and emergency in Medical Unit IV of DHQ Hospital Faisalabad.

Duration of study:

Eighteen months from 15-06-2010 to 14-02-2012

PROCEDURE:

Seventy two patients meeting the inclusion criteria i.e., SLE meeting four classification criteria of the American College of Rheumatology (malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal, neurological, hematological, immunological and antinuclear antibody, disorders).Biochemistry for documenting the following: Incident decrease in renal function as serum creatinine above 1 mg/dl, proteinurea defined as more than 500mg of protein in 24 hours, urine microscopic hematuria as defined >5 RBC / HPF, presence of cellular casts (WBC or RBC casts) were selected from OPD and emergency in Medical Unit IV of DHQHospital after approval of Hospital ethical committee and taking informed written consent. The purpose of research was explained to the patients.

Patients having creatinine clearance below 30 ml/min, serum creatinine above 3mg/dl, taking immunosuppresant therapy, monoclonal antibody therapy within past 30 days and pregnant and lactating women were excluded from study.

Risks like infections, gastrointestinal side effects (nausea, vomiting, diarrhoea) neutropenia rashes and benefits like induction of remission and decreasing relapse rate was discussed with the patient.

After confirmation of lupus nephritis the cases were allocated randomly to two groups, group A having 36 patients and group B having 36 patients.

Group A:

Group A received MMF orally at a initial dose of 500mg twice daily and then dose was increased to 750mg twice daily at week 2 and increased weekly to a maximum dose of 1000mg three times/day unless the WBC fall below 3000/mm^3.

Group B:

Group B received intravenous CYC as monthly pulses of 0.5 g/m^2 body surface area as initial dose and then 1 gm/m^2 body surface area. Dose was modified on the basis WBC count, which must be above 2000/mm^3

Both groups received prednisolone at a dose of 1mg/kg/day with tapering by 10-20% at one week or two week intervals on the basis of clinical improvement. The new appearance or worsening of manifestation of extra renal disease could be treated with one pulse of intravenous methylprednisolone for three-days or increase doses of prednisolone to a maximum of 2 mg/kg/day. Data was collected on especially designed proforma attached hereby observations regarding efficacy

included all the number of cases in which complete remission of disease was noted in 24 weeks, defined as the return to within 10% of normal values of serum creatinine levels, proteinurea and urine sediment.

STATISTICAL ANALYSIS:

Data was entered into SPSS version 10 and analyzed. Descriptive statistics was included by calculating mean and standard deviation for quantitative data i.e. age and frequency / percentages were calculated for qualitative data i.e. sex and efficacy (complete remission of disease). Chi Square test was used to compare the efficacy of two drugs based on remission after 24 weeks. P value of ≤ 0.05 was taken as significant.

RESULTS:

The mean age of the patients in group A was 27.6±5.0 years and in group B was 28.4±4.9 years. In group A, there were 14 (38.9%) patients in the age range of 20-25 years, 13 (36.1%) patients in the age range of 26-30 years, 5 (13.9%) patients in the age range of 31-35 years and 4 (11.1%) patients in the age range of 36-40 years. In group B, there were 11 (30.6%) patients in the age range of 20-25 years, 15 (41.7%) patients in the age range of 26-30 years, 5 (13.9%) patients in the age range of 31-35 years and 5 (13.9%) patients in the age range of 36-40 years.In group A, there were 3 (8.3%) male patients and 33 (91.7%) female patients. In group B, there were 36 (100%) female patients.In group A, 9 (25%) patients had complete remission after 24 weeks of treatment and in group B, 2 (5.6%) patients had complete remission after 24 weeks of treatment (Table 1).In group A, the mean serum creatinine before treatment was 1.9±0.4 mg/dl and in group B was 2.0±0.4 mg/dl (Table 2). In group A, the mean proteinuria before treatment was 3.0±0.6 (gm/24hr urine) and in group B was 2.8±0.6 (gm/24hr urine) (Table 3). In both groups urine sediment before treatment was positive in 36 (100%) patients (Table 4).In group A, the mean serum creatinine after treatment was 1.8±0.4 mg/dl and in group B was 1.9±0.4 mg/dl (Table 5). In group A, the mean proteinuria after treatment was 2.4±0.7 (gm/24hr urine) and in group B was 2.8±0.6 (gm/24hr urine) (Table 6). In group A there were 28 (77.8%) patients had positive urine sediment after treatment and in group B there were 34 (94.4%) patients had positive urine sediment after treatment (Table 7).

Table 1: Distribution of patients by efficacy

Efficacy	Group A (n=36)		Group B (n=36)	
	No.	Percentage	No.	Percentage
Yes	9	25.0	2	5.6
No	27	75.0	34	94.4
χ^2	7.8			
Df	1			
P	0.03			

Key: n Number of patients

Table 2: Distribution of patients by serum creatinine before treatment

Serum creatinine (mg/dl)	Group A (n=36)		Group B (n=36)	
	No.	%	No.	%
1.5-2.0	23	63.9	22	61.1
2.1-2.5	13	36.1	8	22.2
2.6-3.0	0	0	6	16.7
Mean±SD	1.9±0.4		2.0±0.4	

Key: n Number of patients
SD Standard deviation

Table 3: Distribution of patients by proteinuria before treatment

Proteinuria (gm/24hr urine)	Group A (n=36)		Group B (n=36)	
	No.	%	No.	%
2.0-3.0	21	58.3	25	69.4
3.1-4.0	15	41.7	11	30.6
Mean±SD	3.0±0.6		2.8±0.6	

Key: n Number of patients
SD Standard deviation

Table 4: Distribution of patients by urine sediment before treatment

Urine sediment	Group A (n=36)		Group B (n=36)	
	No.	Percentage	No.	Percentage
Positive	36	100.0	36	100.0
Negative	0	0	0	0

Key: n Number of patients

Table 5: Distribution of patients by serum creatinine after 24 weeks of treatment

Serum creatinine (mg/dl)	Group A (n=36)		Group B (n=36)	
	No.	%	No.	%
1.0-1.5	19	52.8	8	22.2
1.5-2.0	6	16.6	15	41.7
2.1-2.5	11	30.6	13	36.1
Mean±SD	1.8±0.4		1.9±0.4	

Key: n Number of patients
SD Standard deviation

Table 6: Distribution of patients by proteinuriaafter 24 weeks of treatment

Proteinuria (gm/24hr urine)	Group A (n=36)		Group B (n=36)	
	No.	Percentage	No.	Percentage
1.5-2.0	11	30.6	4	11.1
2.0-3.0	20	55.5	21	58.3
3.1-4.0	5	13.9	11	30.6
Mean±SD	2.4±0.7		2.8±0.6	

Key: n Number of patients
SD Standard deviation

Table 7: Distribution of patients by urine sediment after 24 weeks of treatment

Urine sediment	Group A (n=36)		Group B (n=36)	
	No.	Percentage	No.	Percentage
Positive	28	77.8	34	94.4
Negative	8	22.2	2	5.6

Key: n Number of patients

DISCUSSION:

Recent trial of 24 weeks has found mycophenolatemofetyl to be more effective than intravenous cyclophosphamide in inducing remission which showed 16 of 71 patients (22.5%) receiving mycophenolatemofetyl and 4 of 69 patients (5.8%) receiving cyclophosphamide had complete remission.[7]In our study the mean age and sex distribution of the patients is comparable with the study of Ginzleret al.[7]In our study, in group A, the mean serum creatinine before treatment was 1.9±0.4 mg/dl and in group B was 2.0±0.4 mg/dl. As compared with the study of Ginzleret al[7] in MMFgroup the mean serum creatinine before treatment was 1.06±0.5 mg/dl and in CYC group the mean serum creatinine before treatment was 1.08±0.5 mg/dl, which is comparable with our study.In our study, in group A, the mean proteinuria before treatment was 3.0±0.6 (gm/24hr urine) and in group B was 2.8±0.6 (gm/24hr urine). As compared with the study of Ginzler et al[7] in MMFgroup the mean proteinuria before treatment was 4.1±3.1 (gm/24 hr urine) and in CYC group the mean proteinuria before treatment was 4.4±3.5 (gm/24hr urine), which is comparable with our study.In our study, in group A, the mean serum creatinine after treatment was 1.8±0.4 mg/dl and in group B was 1.9±0.4 mg/dl. As compared with the study of Ginzleret al[7] in MMFgroup the mean serum creatinine after treatment was 1.0±0.4 mg/dl and in CYC group the mean serum creatinine after treatment was 1.0±0.4 mg/dl, which is comparable with our study.In our study, in group A, the mean proteinuria after treatment was 2.4±0.7 (gm/24hr urine) and in group B was 2.8±0.7 (gm/24hr urine). As compared with the study of Ginzler et al[7] in MMFgroup the mean proteinuria after treatment was 2.5±3.0 (gm/24 hr urine) and in CYC group the mean proteinuria after treatment was 2.9±3.0 (gm/24hr urine), which is comparable with our study.In our study in group A, 25% patients had complete remission in 24 weeks of treatment and in group B, 5.6% patients had complete remission in 24 weeks of treatment. As compared with the study of Ginzleret al[7] in MMFgroup 22.5% patients had complete remission in 24 weeks of treatment and in CYC group 5.8% patients had complete remission in 24 weeks of treatment, which is comparable with our study.Two randomized studies comparingMMF with CYC for lupus nephritiswere reported. Chan et al[9] reported on a 12-month study involving42 patients with class IV nephritis in which MMFwas as effective as oral CYC in inducing remission.In their study, the rate of infectious complications was similarin the two treatment groups, but only patients treated withCYC had amenorrhea, alopecia, or leucopenia, ordied.Mak, A et al. showed MMF has comparable efficacy to CYC in inducing complete and partial renal remission,

preventing ESRD and reducing mortality and a lower incidence of adverse events in patients with lupus nephritis.[10]Long-term experience in clinicaltrials using intravenous CYC shows a relapse rateof up to 45 percent in patients with proliferative lupus nephritis,despite a complete clinical response to induction therapy.[11]Furthermore, the type of maintenance therapy after successfulintravenous CYC appears to be important; Contreraset al[8] found the composite end point of death or chronic renalfailure and the rate of relapse-free survival to be significantlyhigher with MMF than with CYC.[12]Hospitalizations, amenorrhea, infections, and upper gastrointestinalsymptoms were also significantly less frequent with MMF than with CYC.

On the above discussion it is concluded that, induction therapy with MMF wassuperior to intravenous CYC in inducing completeremission of lupus nephritis in this study. MMFappeared to be better tolerated than CYC. Unresolvedissues include determining the flare rate after induction withMMF, as compared with that for CYC,and determining the appropriate dose and duration of MMF maintenance therapy.

CONCLUSION:

It is concluded from this study that mycophenolatemofetyl administered orally is superior in efficacy to intravenous cyclophosphamide in the management of lupus nephritis and almost comparable results obtained with other studies.

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