

Mycophenolate mofetil vs. cyclophosphamide-based induction regimens for lupus nephritis: Outcomes at a tertiary care centre in Lahore, Pakistan

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Abstract

Objective: To compare the efficacy of mycophenolate mofetil with intravenous cyclophosphamide induction therapy in lupus nephritis.

Method: The observational, prospective, cohort study was conducted at the Rheumatology Department of Fatima Memorial Hospital, Lahore, Pakistan, from July 2016 to June 2019, and comprised lupus nephritis patients. For induction therapy, the patients were assigned at the discretion of the treating rheumatologist to mycophenolate mofetil group MMF, and intravenous cyclophosphamide group CYC. The latter group was further divided into NIH subgroup that received the therapy as per the protocol of the National Institutes of Health, and ELNT subgroup which received the therapy as per the Euro Lupus Nephritis Trial protocol. Maintenance therapy in all groups was mycophenolate mofetil. Tacrolimus was added in case of non-response. The outcome was the achievement of complete renal response at 6, 12 and 24 months. Data was analysed using SPSS 26.

Results: Of the 131 patients, 126(96.2%) were females. The overall mean age was 27 ± 7.7 years. There were 58(44.2%) patients in group MMF and 73(55.7%) in group CYC, which had subgroup NIH 46(63%) and subgroup ELNT 27(37%). The complete renal response rates at 6, 12, and 24 months were 22 (43.1%), 35 (71.4%), and 40(83.3%) for group MMF; 5(12.5%), 9(22%) and 24 (58.5%) for subgroup NIH, and 6(26.1%), 8(36.4%) and 14(63.6%) for subgroup ELNT. Group MMF outcomes were significantly better than the rest ($p < 0.05$).

Conclusion: Mycophenolate mofetil induction therapy was more effective than intravenous cyclophosphamide in terms of achieving remission at 6, 12 and 24 months.

Keywords: Systemic lupus erythematosus, Lupus nephritis, Mycophenolate mofetil, Cyclophosphamide.

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Introduction

Systemic lupus erythematosus (SLE) is a multi-system disease affecting predominantly women of childbearing age.¹ Renal involvement occurs in ~60% of patients with SLE and is associated with significant morbidity and mortality.² Over the last four decades, advances in treatment regimens with high-dose corticosteroids, intravenous (IV) cyclophosphamide (CYC) or mycophenolate mofetil (MMF) have led to improved outcomes.³ However, discrepancies are reported in the incidence and outcomes of lupus nephritis (LN) among various ethnicities. The data from the United States showed that Black and Asian lupus patients have the highest incidence of LN, followed by Hispanics.² Black and Hispanic LN patients have worse outcomes and are more likely to progress to end-stage renal disease (ESRD) than white patients.^{4,5} The response to treatment also seems to differ by race and ethnicity, as evident from the post-hoc analysis of the Aspreva Lupus Management Study (ALMS) study Department of Rheumatology, Fatima Memorial Hospital, College of Medicine and Dentistry, Lahore, Pakistan.

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that more Black and Hispanic patients responded to MMF than IV CYC.⁶

The comparison between two induction treatments was replicated in several global lupus cohorts.^{7,8} The results underscored the interaction between response to a particular treatment regimen and the ethnic background of the target population.^{7,8} The region of South Asia consists of seven countries, including Pakistan. There is a paucity of data about the incidence, outcomes and response to various treatment regimens for LN in the ethnically distinct population from this region. Renal involvement in SLE patients from Pakistan is estimated to be around 50%, with most of the patients reported having Class IV (84%) LN.⁹ The treatment of these patients is based on the results extrapolated from the studies done on populations with genetic backgrounds vastly different from those of the South Asian region. In addition, social and economic factors unique to this region may influence the outcome of a particular treatment regimen.

The current study was planned to compare the efficacy of MMF with IV CYC induction therapy in LN.

Materials and Methods

The observational, prospective, cohort study was

conducted at the Rheumatology Department of Fatima Memorial Hospital, Lahore, Pakistan, from July 2016 to June 2019 and comprised lupus nephritis patients. The study was designed on the model of comparative effectiveness research (CER) initiative to generate data specific to the Pakistani population and ultimately improve patient outcomes.¹⁰ Approval was obtained from the institutional ethics review board (IRB), and the study was conducted in accordance with the International Council for Harmonisation (ICH) guidelines.¹¹

All LN patients met the American College of Rheumatology (ACR) for the classification of SLE or the Systemic Lupus International Collaborating Clinics (SLICC-12) criteria.¹² LN was diagnosed either by renal biopsy or based on persistent proteinuria ≥ 0.5 gm per 24 hrs or urinary protein-to-creatinine ratio (UPCR) of ≥ 0.5 gm/gm with or without the presence of active urinary sediment on two consecutive samples within six weeks.¹³ Patients with inconsistent follow-ups or who were non-compliant with their medications were excluded. Patients were followed up as per the standard of care guidelines for the treatment of LN as recommended by the European League Against Rheumatism (EULAR), European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and the ACR.^{13,14} Patient demographics, renal biopsy (when available), assigned treatment regimen, and laboratory values were recorded at the baseline. At each follow-up visit, compliance with treatment and laboratory data were recorded. Renal biopsies were performed and processed as per the standard protocol and reported by pathologists who were not associated with the study.

The attending rheumatologist's clinical judgment and patient preference were the bases for assigning treatment regimens. For induction therapy, the patients were assigned to IV CYC group which was further divided into NIH subgroup that received the therapy as per the protocol of the National Institute of Health (NIH) comprising IV CYC at a dose of 500-1000mg/m² of body surface area for six months¹⁵ and ELNT subgroup which received the therapy as per the Euro Lupus Nephritis Trial protocol comprising IV CYC 500mg every two weeks for three months.¹⁶ The MMF group received oral dose titrated up to 2-3 gm/day as tolerated for six months.¹⁷

All induction therapy regimes included IV methylprednisolone of 3gm at the start, followed by oral prednisolone 0.5mg/kg/day/30 days and tapered over the next two months to 10mg/day or less as clinically indicated. All patients received oral hydroxychloroquine, which was titrated to 5-6 mg/kg/day.¹⁸ Patients were started on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as well unless

contraindicated.

Patients without complete renal response (CRR) or partial renal response (PRR) after six months of induction were treated by switching the induction regimen from IV CYC to MMF or vice versa.¹² Besides, rituximab 375mg/m² was allowed as rescue therapy in high-risk nephritis patients, with high baseline creatinine, and failure to respond to initial inductions with either CYC or MMF.¹⁶

All patients in the MMF group continued it beyond six months of induction as maintenance. Patients in NIH and ELNT subgroups were switched to MMF after 6 and 3 months of induction as per the relevant protocol.^{15,16} Maintenance dose of MMF titrated up to 2gm/day. In addition, tacrolimus (TAC) 0.05mg/kg/day was added to MMF, or the patient was switched to TAC in case of intolerance or flare.

Flare was defined as a rise in UPCR of >1 in the previously normalised ratio. Flares during the induction phase were treated with IV methylprednisone 500-1,000mg and/or rituximab, while flares during the maintenance phase were treated with a single dose of 500mg IV methylprednisolone.¹⁸

The primary outcome was CRR determined after 6 and 12 months of therapy, while the secondary outcome was CRR at 24 months.

CRR was defined as proteinuria <0.5 gm/day or UPCR <0.5 mg/mg with normal serum creatinine.

CRR and PRR were calculated using censored rates, i.e., patients lost to follow-up or had changes in a treatment plan were not included in the efficacy analysis. In addition, survival analysis was done based on the development of ESRD requiring dialysis, or death occurring during the 24 months of the study. Patients lost to follow-up were not included in the efficacy and survival analysis.

Data was analysed in SPSS 26. Data was reported as frequencies and percentages, mean \pm standard SD and median with interquartile range (IQR), as appropriate. Comparison of intergroup mean values was done using analysis of variance (ANOVA), while median values were compared using Wilcoxon rank sum test. Chi-square test was applied where necessary. $P < 0.05$ was considered significant.

Results

Of the 131 patients, 126(96.2%) were females. The overall mean age was 27 ± 7.7 years. Antinuclear antibody (ANA) by indirect immunofluorescent assay (IFA) was positive in 128(98.1%); the record was missing in the remaining

Table-1: Baseline characteristics.

Characteristic	MMF (n=58)	NIH (n=46)	ELNT (n=27)	p-value
Age Median (IQR) (years)	28.00 (9.50)	25.50 (10.25)	23.00 (10.00)	0.053
Female n (%)	56(96.6)	43 (93.5)	26 (96.3)	0.694
Baseline UPCr mg/mg Mean±SD	3.27 ± 4.33	3.42 ± 3.09	4.31 ± 5.06	0.712
Baseline creatinine Mean±SD	0.935 ± 0.60	1.1 ± 0.73	1.16 ± 0.72	0.279
Frequency of patients with Raised creatinine more than 1.2mg/dl n (%)	7 (12.1)	11 (23.9)	8 (29.6)	0.116
Biopsy class n (%)				0.014
Class III/III+V	12(20.7)	9 (19.6)	5 (18.5)	
Class IV/IV+V	17(29.3)	27 (58.7)	17 (63)	
Class V alone	6(10.3)	3 (6.5)	2 (7.4)	
Not Done	23 (39.7)	7 (15.2)	3 (11.1)	
Activity index BX Mean±SD	4.50±1.97	6.14 ± 2.96	5.53 ± 2.83	0.256
Chronic index BX Mean±SD	3.25±2.9	3.00 ± 1.82	3.24 ± 2.51	0.935

CYC: Cyclophosphamide, MMF: Mycophenolate Mofetil, NIH: National Institutes of Health, ELNT: Euro lupus nephritis trial, UPCr: Urinary protein-to-creatinine ratio, SD: Standard deviation, IQR: Interquartile range, BX: Renal biopsy.

Table-2: Intergroup comparison.

Renal response n (%)	MMF (n=58)	NIH n=46)	ELNT (n=27)	p-values
CRR 6 months (n=114)*	22/51 (43.1)	5/40(12.5)	6/23(26.1)	0.006
CRR 12 months (n=112)*	35/49 (71.4)	9/41 (22.0)	8/22(36.4)	0.000
CRR 24 months (n=111)*	40/48(83)	24/41(58.5)	14/22 (63.6)	0.029
MMF maintenance Dose in grams±SD	1.75±0.53	1.92±0.63	1.82±0.59	0.369
Duration of Maintenance therapy in months±SD	22.7±14.6	31.97±17.1	21.75±13.89	0.007
Prednisone dose as per the last visit in mg±SD	5.3±4.08	6.58±3.60	11.5±8.4	0.002
Last Follow-up creatinine above normal (n=129)	5/57 (8.8)	12/45 (26.7)	4/27 (14.8)	0.051
Missing data or lost to follow-up n=17	7 (12.1)	7 (15.2)	3 (11.1)	0.848

* percentages for each subgroup were calculated on the basis of complete for that particular visit. NIH: National Institutes of Health, MMF: Mycophenolate mofetil, ELNT: Euro lupus nephritis trial, CRR: Complete renal response.

4(1.9%) cases. Data on Anti-double-stranded deoxyribonucleic acid (anti-ds-DNA) was available in 77 (58.7 %) at baseline and and out of them it was positive in 75 (97.4 %) of cases . Similarly data on Complement levels was available only in 48 (36.6 %) at baseline at it was found to be low in 33 (68.8 %). At baseline, 26(19.8 %) out of 131 patients had a raised serum creatinine level. Data on 24 hrs urinary protein or UPCr was available in 93 (70.9 %) and Nephrotic range proteinuria amongst them was found to be in 36 (38.7 %).

There was 58(44.2%) patients in group MMF and 73(55.7%) in group CYC, which had subgroup NIH 46(63%) and subgroup ELNT 27(37%). The MMF group patients were older than the rest ($p=0.035$). There were no other differences among the groups regarding baseline characteristics except for fewer patients with class IV LN in the MMF group ($p=0.014$). There were 101(77%) patients

who underwent a renal biopsy.

Out of the total cohort, data on CRR at 6, 12 and 24 months was available in 114(87%), 112(85.5%), and 111(84.7%) patients. Of them, CRR was achieved in 33(28.9%) at 6 months, 52(46.4%) at 12 months, and 78(70.3%) at 24 months. Complete renal response rates at 6, 12, and 24 months in the three treatment groups were achieved in 22 (43.1%), 35 (71.4%), and 40(83.3%) in LN patients in MMF group; 5(12.5%), 9(22%) and 24 (58.5%) in NIH, and 6(26.1%), 8(36.4%) and 14(63.6%) in ELNT groups, respectively. The intergroup differences were significant (Table 2).

There were more patients in NIH group 12 (26.7%) and ELNT group 4 (14.8%) compared to MMF group 5 (8.8%) with creatinine above 1.2mg/dl cut-off at the last follow-up ($p=0.05$, LR: 5.89). There were total 3/131 (2.3 %) patients who developed end stage renal failure and were on dialysis in the whole cohort, none in MMF, 1(2.2 %) in NIH and 2(7.4%) in ELNT groups. There were 5(3.8 %) patients out of 131 who were not traceable at the time of analysis, and their data was excluded from survival analysis; 1 (1.7 %) in MMF, and 2 (4.3 %) in NIH and 2 (7.4 %) ELNT groups.

Rituximab was given to 8 (6.1 %) patients who were MMF/CYC non-responders or were intolerant to MMF or CYC; CRR was achieved in 3(37.5%) and 4(50%) patients at 6 and 12 months, respectively, and there was sustained renal response up to 2 years. Out of 8 patients, 2(25 %) needed haemodialysis.

MMF was given as maintenance therapy in 90(68.7%) patients. There were 23(17.4%) patients who received MMF+TAC. There were 6 (4.5 %) patients receiving either TAC 4 (3.0 %) or azathioprine 2 (1.5 %) as maintenance therapy who were not included in the analysis.

Discussion

To the best of our knowledge, the current study is the first comparative analysis of the three induction regimens of an LN cohort with a follow-up of 2 years from Pakistan. Immunosuppressive treatment regimens used in the cohort were as per the standard guidelines.^{13,17} There were no significant differences in baseline characteristics

amongst the three groups except that patients were more likely to be assigned to CYC-based regimens by the treating rheumatologist in case they had class IV disease, most likely due to the selection bias which can be avoided in future by randomisation.

The overall efficacy of MMF was superior to both CYC groups at 6, 12 and 24 months. However, the CRR rates improved at 12 and 24 months in CYC groups, possibly because of the confounding effect of using MMF as maintenance therapy in all groups. This highlights that MMF-based induction and maintenance was a viable strategy in Pakistani LN patients. Besides, amongst CYC ELNT regimen dose was as efficacious as CYC NIH dose in achieving renal responses and maintaining stable creatinine, making it a second viable option with less toxicity.

Azathioprine had been used only in 1.5% of the patients in the study and they were excluded from analysis, as with the advent of MMF, this drug is no more a preferred choice due to the associated risk of increased rates of relapse.¹⁸

A recent randomised open-label study from a tertiary care setting in Rawalpindi, Pakistan, comparing MMF with NIH regimen did not show any significant difference in renal response rates in the two groups.¹⁹ However, it was a small study with 14 patients in each treatment group, and reported only short-term renal response rates.

Similarly, another randomised, open-label 24-week study from Pune, India, comparing MMF (n=17) with IV CYC as per NIH (n=23), showed comparable efficacy in CRR 52.9% vs. 47.8% at 24 weeks. However, in the current study, CRR at 24 weeks was 43%, 12.5%, and 26.1% in MMF, NIH and ELNT groups, respectively.²⁰

A retrospective study reporting long-term outcomes of patients with LN treated with MMF and CYC-based regimens from India showed comparable renal and patient survival at two years and beyond.²¹ A randomised control trial using low-dose MMF compared to CYC in Nepal also showed comparable efficacy, highlighting that compared to Caucasians, low dosages of MMF in South Asians might be equally effective.²²

In the current study, a low dose of CYC was equally efficacious in achieving all the renal outcomes compared to a high dose of CYC, a finding reported earlier.²³ There are very few studies on head-to-head comparison between ELNT and MMF. One report from India showed comparable efficacy.²⁴

A recent systematic review about the 2019 update of the joint EULAR and ERA-EDTA recommendations supports

high-quality evidence for MMF and mycophenolic acid (MPA) and low-dose CYC induction therapies.²⁵ This update also emphasises timelines of achieving the targets, which is in line with the current findings.

MMF as maintenance therapy in the current study showed consistent findings of maintaining CRR of around 60% at 24 months in both CYC groups, close to the findings of Kabbalo et al. (56% at 29 months of follow-up).²⁶ That study, however, did not elaborate on the efficacy of sustaining the complete response.²⁶

In the cohort, adding TAC to MMF in maintenance therapy benefited disease flares and achieving remission. Yap et al. reported 66.7% and 80% response rates after 12 and 24 months of add-on TAC treatment, respectively.²⁷

The current study used rituximab in 8 patients with high-risk factors at baseline and who relapsed or did not respond to induction therapy. Rituximab, by achieving 50% CRR by 12 months and stabilising renal creatinine in 75% of high-risk cases. Despite the failure of a trial, rituximab was found to be efficacious in refractory cases.²⁸

The current study has limitations. First, it was an open-label, nonrandomised comparative single-centre study. Therefore, selection bias may have occurred. Second, the study used per-protocol data for analysing primary outcomes rather than an intention-to-treat analysis as patients who were lost to follow-up due to non-compliance or had missing data were excluded. Third, the study did not use clinical activity parameters, and the adverse events data was not reported as it was scarce. Multi-centre, randomised controlled trials are recommended to compare the three induction regimens' efficacy and safety profile.

Many resource-constraint settings might prefer CYC-based regimens, but a recent analysis of the cost-effectiveness of various LN induction and maintenance therapies found that even though MMF-based induction and maintenance was expensive, it was superior in terms of remission rates, risks of ESRD, all-cause mortality, and quality of life.²⁹

Conclusion

MMF was more efficacious for induction as well as maintenance therapy of LN in terms of achieving CRR at 6 and 12 months that was sustained up to 24 months.

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Author Contribution:

MAS: Data concept, aquisition, analysis, drafting, final approval.

AK: Data aquisition, analysis, drafting, final approval.

FN: Data aquisition, drafting, final approval.

NMA: Concept, critically reviewing, intellectual input and final approval.