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Comparison between oral Mycophenolate Mofetil and intravenous Cyclophosphamide for the treatment of the lupus nephritis patients

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Abstract: Lupus nephritis (LN) is a serious type of systemic lupus erythematosus (SLE) that can cause renal failure and death. The goal of this research was to look at the efficacy and safety of intravenous cyclophosphamide (ivCYC) and oral mycophenolate mofetil (MMF) for lupus nephritis induction and maintenance therapy**.** Thirty-eight patients with proliferative lupus nephritis treated with ivCYC (n = 19) or oral MMF (n = 19) were included in this prospective, randomized, comparative study. The standard of therapy for all patients is oral methylprednisolone (1 mg/kg/day), in addition to either oral MMF (2 g/kg/day) for six months or iv-CYC 500 mg every 14 days for six months. Hemoglobin (Hb), serum albumin (sAlb), serum creatinine_(sCR), albumin to creatinine ratio (Alb/Cr ratio) , and erythrocyte sedimentation rate (ESR)were measured before and after therapy for participants in both groups. The 19 patients who received MMF had an average age of 31.6± 5.93 years. The mean age of the 19 patients who received ivCYC pulses was 24.95± 3.57 years. Both groups showed a significant difference (P <0.05) before and after laboratory analysis. In comparison, there was no significant variance (P> 0.05) between patients treated with ivCYC and those treated with MMF. By using both therapies, both groups demonstrate considerable improvement. Oral MMF was shown to be equally effective as iv CYC in the long-term therapy of lupus nephritis, with no significant changes in the rate of laboratory testing between the two regimens.

Keywords: Systemic lupus erythematosus, lupus nephritis, cyclophosphamide, mycophenolate mofetil**,** hemorrhagic cystitis.

1. INTRODUCTION

Systemic lupus erythematosus (SLE)is an autoimmune disease marked by the production of autoantibodies and deposition of immune complexes containing complements. Inflammation and damage result from activation, within the tissue that is affected [1,2].

SLE can be identified by several clinical symptoms, including skin, joint, kidney, and central nervous system manifestations, as well as serological results, such as anti-nuclear antibodies (ANA)[3]. Because organ system involvement and clinical and serological manifestations vary widely across patients and within the same patient over time, SLE is an unexpected and challenging illness to manage.[4].

A typical side effect of SLE is lupus nephritis (LN). The progression of SLE will result in clinical signs of renal impairment in about 70% of individuals[5]. An initial decline in renal function or proteinuria was present in 33% of SLE patients[6]. Lower age at diagnosis, male gender, and being Hispanic, Asian, or African are risk factors for LN[7].

Mycophenolate mofetil (MMF)has a strong inhibitory effect on the synthesis of nucleic acids and causes inhibition in activated T and B lymphocytes[8]. It is widely used in LN. Due to its shown effectiveness as a medication for remission induction and maintenance, good tolerability, enteral administration, and minimal gonadal impact[9]. More than 50% of patients experience adverse effects; diarrhea is the most frequent symptom, though it is typically minor; 25% of patients require drug suspension. The most prevalent illnesses, pneumonia (2%), and urinary tract infections (10%) are typically treatable at home[10].

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Intravenous cyclophosphamide (ivCYC),is one of the potent alkylating medications, and is widely used to treat lupus erythematosus, rheumatoid arthritis, multiple sclerosis, sarcoma, bone marrow transplant, and neuroblastoma. [11].

Clinically cyclophosphamide's most prominent side effects include alopecia, immunosuppression (when not wanted), and injury to the bladder (hemorrhagic cystitis). The risk of cardiotoxicity increases when extremely high doses(0.5–1 g/m2)are administered[12]. This study aims to evaluate the effects of MMF compared to CYC for the treatment of LN.

2. METHODS

Thirty-eight female patients with SLE with LN were included in our study and their ages ranged from 20 to 50 years old. They were gathered from the outpatient clinic of Al-Azhar University's Sayed Galal hospital.

The study was designed as a single-center, prospective randomized, –controlled trial.

• The ethical committee of Al-Azhar University's Faculty of Medicine has authorized this study under the number 0000085.

• Informed consent was signed by all patients in the study.

Inclusion criteria were all female patients who had systemic lupus erythematosus with lupus nephritis either newly diagnosed or with a history of SLE with lupus nephritis.

Participants were excluded if the patients had acute inflammatory processes such as rheumatoid arthritis or other rheumatologic diseases) As well as patients who are taking immunosuppressive therapy, malignancies, HCV, HBV, or HIV infection, and all stages of lupus nephritis except stages I, V, and VI.

2.1. Patients Enrollment and Randomization:

Patients were invited to participate during a visit to the outpatient hematology clinic at Sayed Galal hospital of Al-Azhar University. Once they met the inclusion criteria and signed the consent form, the frequency and percentage of renal biopsy stages were recorded. All patients enrolled in this study were subjected to the following investigations: serum creatinine (s-CR), serum albumin (s-Alb), and albumin /creatinine ratio (Alb/Cr ratio) to follow the treatment response and renal outcome. To track the progression of the illness and inflammation, erythrocyte sedimentation rate (ESR) was recorded.

All patients were divided randomly into two groups. Each group had 19 female patients.

The first group received oral prednisolone 1mg/kg/ day (Solupred5mg® Sanofi Aventis) and ivCYC 500 mg (Endoxan N 500 mg®Baxter) once every two weeks for 6 months.

Second group received oral prednisolone (1mg/kg/day) (solupred 5mg®) and oral MMF (2-3g/day(1200mg/m2)) cellceptct 250 mg® Roche) daily for 6 months.

2.2. Data Analysis:

Various tools were used to examine data from 38 patients. Excel 365 was utilized for data entry and data visualization. Before conducting any statistical analysis, the data was cleaned. Data was first investigated using IBM SPSS VER.25. The frequency of the key quantitative variables has been done and descriptive statistics for the key quantitative variables have been also done.

Inferential statistics were employed to address the study's primary questions. All parametric variable assumptions have been checked. The Mann-Whitney test was used to make various comparisons for independent two groups variables while correlated groups were analyzed using the Wilcoxon signed-rank test. Data were presented as mean, and quartiles and P-value were considered significant at < 0.05.

Data were tested for satisfying assumptions of parametric tests, results showed that variables followed a normal distribution pattern, so the parametric protocol of analysis was used. Continuous variables Shapiro- Wilk, and Kolmogorov-Smirnov test results for normality were listed to graphically represent the distribution of all studied factors.

3. RESULTS

First of all, the patient randomly divided into two groups, each group containing 19 patients **(Table 1**), first group (GP1) was treated by ivCYC, while the second group (GP2) was treated by MMF.

Table 1: Mean ± SD and range of age recorded for participant patients in both groups GP1 and GP2:

Stat.	ivCYC (GP1)	MMF(GP2)
Mean ± SD	31.63 ± 5.93	24.95 ± 3.57
Range	20 – 40	19 - 32

As shown in **Table 2** Values shown are mean ± standard deviation (SD), (GP1) iv CYC, (GP2) MMF: serum creatinine(sCr), serum albumin(sALb), the data tested for normality for the parametric analysis of the patients in both groups before being subjected to the treatment protocol. The normality test (Shapiro-Wilk) passed with ($P > 0.05$) and the equal variance test (Brown-Forsythe) passed with

(*p*> 0.05). After accounting for the impacts of parameter changes, the difference in mean values between the various levels of treatment (GP1 and GP2) is not large enough to eliminate the possibility that the discrepancy is attributable to random sampling variability. The difference is not statistically significant (P = 0.641). Similarly, the effect of varying degrees of treatment is independent of the level of Parameter present. treatment and parameter had no statistically significant interaction (P = 0.934).

Table 2: Laboratory tests performed for the patients in (GP1) before being subjected to the ivCYC and MMF treatment protocol

Treatment	Parameters		
Iv CYC	**Hb**	**Mean±SD**	11.16±0.91
		Range	10-12.5
	sALb	**Mean±SD**	3.06±0.48
		Range	2.1-4
	sCr	**Mean±SD**	2.24±0.91
		Range	1.3-4.5
	Alb/Cr ratio	**Mean±SD**	3561.05±1287.23
		Range	1600-5450
	ESR	**Mean±SD**	98.84±17.84
		Range	70-150
MMF	**Hb**	Mean±SD	11.45±0.71
		Range	10-12
	Albumin	**Mean±SD**	3.09±0.55
		Range	2-4.2
	Creatinine	**Mean±SD**	1.97±0.51
		Range	0.9-3.1
	Alb/Cr ratio	**Mean±SD**	3796.84±1835.19
		Range	1850-8670
	ESR	**Mean±SD**	103.32±13.98
		Range	70-140

Hb: Hemoglobin, **sAlb**: serum albumin, **sCR**: serum creatinine, **Alb/Cr ratio**: albumin to creatinine ratio., and **ESR**: Erythrocyte sedimentation rate.

The Holm-Sidak method was used for all Pairwise Multiple Comparison Procedures, with an overall significance threshold of = 0.05. There was no significant differentiation (*P*> 0.05) between opposite parameters as shown that Hb in comparison between GP1 Vs GP2 was not significant with *P*-value= 0.999. At the same page, sALb, sCr, Alb/Cr ratio and ESR in comparison between GP1 Vs GP2 there were not significant differentiation with *P*-value= 1; 0.999; 0.307 and 0.985 respectively.

As shown in **(Tables 2 and Figures 1-supplementary)** Hb; sCr, Alb/Cr ratio, and ESR display a significant decrease after treatment by ivCYC, another page Albumin shows a significant increase after treatment.

A recorded decrease in Hb; Creatinine; Alb/Cr ratio and ESR tested the treatment of the patient in GP1 with ivCYC by -14.2; -30.6; -72.1 and -56%. On the other hand, an increase in albumin value by 24% was noticed **(Figure 2- supplementary).**

Radar charts **(Figure 3- supplementary)** represent the individual increase and decrease of laboratory parameters tested for patients treated by ivCYC before and after treatment. Revealing the significant improvement of using ivCYC for patients suffering from Lupus nephritis. As shown in Tables 2 &4 the GP1 after subjected to the ivCYC treatment protocol. There was a significant improvement in patient-tested parameters. A paired t-test analysis before and after treatment was used. The normality test (Shapiro-Wilk) was passed for all opposite parameters with p= 0.111; 0.057; 0.269; 0.546 and 0.191 for Hb; Albumin; Creatinine; Alb/Cr ration and ESR respectively.

The treatment effect on the recorded value of Hb; sALb; sCr; Alb/Cr ration and ESR after treatment exceeds the sample mean tested for these values before the treatment application by an amount that is greater than would be expected by chance, rejecting the hypothesis that the population means of Hb; sALb; sCr; Alb/Cr ration and ESR after treatment is greater than or equal to the population mean of them before treatment (P = <0.001).

As shown in **(Tables 2 & 4; and Figure 4-supplementary)** Hb; sCr; Alb/Cr ratio and ESR show a decrease after treatment by MMF. On another page, Albumin shows an increase from 3.06 to 3.8 after treatment.

A recorded decrease in Hb; sCr; Alb/Cr ratio and ESR tested the treatment of the patient in GP2 with MMF by -13; -27.5; -80.6 and -45.8%. On the other hand, an increase in Albumin value by 22% was noticed **(Figure 5- supplementary).**

Table 3: Laboratory tests performed for the patients in (GP1) after being subjected to the iv CYC treatment protocol.

Treatment	Parameters		
IvCYC	Hb	Mean±SD	9.57±1.04
		Range	7.5-11
	SALb	Mean±SD	3.8±0.58
		Range	2.5-4.4
	sCr	Mean±SD	1.56±0.60
		Range	0.9-3.1
	Alb/Cr ratio	Mean±SD	993.68±1364.70
		Range	120-4740
	ESR	Mean±SD	43.47±30.77
		Range	10-140

Hb: Hemoglobin, **sAlb:** serum albumin, **sCR:** serum creatinine, **Alb/Cr ratio**: albumin to creatinine ratio., and **ESR**: Erythrocyte sedimentation rate.

Table 4: Laboratory tests performed for the patients in (GP2) after being subjected to the MMF treatment protocol.

Treatment	Parameters		
MMF	Hb	Mean±SD	9.96±0.96
		Range	1.3-4.5
	sCr	Mean±SD	1.43±0.62
		Range	0.8-3.1
	Alb/Cr ration	Mean±SD	735.2±1002.11
		Range	80-3440
	sAlb	Mean±SD	3.77±0.52
		Range	2.6-4.65
	ESR	Mean±SD	56±26.21
		Range	20-100

Radar charts **(Figure, 6- supplementary)** represent the individual increase and decrease of laboratory parameters tested for patients treated by MMF before and after treatment. Revealing the significant improvement of using ivCYC for patients suffering from Lupus nephritis. As shown in tables **2 & 4** the GP2 after subjected to MMF treatment protocol. There was a significant improvement in patient-tested parameters. A paired t-test analysis before and after treatment was used. The normality test (Shapiro-Wilk) was passed for all opposite parameters with p= 0.177; 0.956; 0.196; 0.514 and 0.347 for Hb; sAlb; sCr; Alb/Cr ration and ESR respectively.

The treatment effect on the recorded value of Hb; Albumin; Creatinine; Alb/Cr ration and ESR after treatment exceeds the sample mean tested for these values before the treatment application by an amount that is greater than would be expected by chance, rejecting the hypothesis that the population means of Hb; sAlb; sCr; Alb/Cr ration and ESR after treatment is greater than or equal to the population mean of them before treatment (P = <0.001).

In comparison between the groups treated with CYC and, MMF. Hb recorded 9.57 and 9.96 for iv CYC and oral MMF respectively. In the same manner. sAlb recorded 3.8 and 3.77; sCr 1.56 and 1.43; Alb/Cr ratio 993.68 and 735.32 and ESR reported 43.47 and 56 for ivCYC and MMF respectively **(Figure 7& 8- supplementary)**.

Figure 9- supplementary represents the Arrow chart which shows the increase and decrease percentage reported for tested parameters for the patient treated by ivCYC and MMF. As shown, sAlb; sCr and Alb/Cr ratio show a decrease in MMF which was reported from ivCYC by -2.8; -8.3, and -26% respectively. On the other hand. an increase in Hb and ESR in the MMF group which was reported from the ivCYC group by 4 and 29% respectively. **Figure, 10- supplementary** represents the principal component analysis PCA ordination which simulates the patient treated by ivCYC and MMF treatment in concern to the result reported by the tested laboratory parameters after treatment. Revealing that, the reported laboratory result for both patient groups lead in distinctive order of each treatment group into two

mean distinctive clusters one for each treatment group and a third small cluster containing 4 patients from the ivCYC group in another dimension. This reveals an observed differentiation recorded for patients treated with two different treatments (ivCYC and MMF).

Finally, there was a differentiation in the laboratory parameter tested for patients after being treated by ivCYC and MMF. But this differentiation was not significant in the long-term treatment of lupus nephritis.

4. DISCUSSION

Lupus nephritis is one of the most serious symptoms of SLE, with significant morbidity and death. This condition affects several organs, including the kidney, lungs, and neurological system.[13,14] For lupus nephritis, many therapy regimens have been proposed. Immunosuppressive glucocorticoid regimens paired with cytotoxic medicines, notably ivCYC, are useful for treating severe proliferative lupus nephritis. [13,15] ivCYC, On the other hand, has been associated with adverse effects such as bone marrow suppression, amenorrhea, sterility, an increased risk of infections, hemorrhagic cystitis, bladder cancer, leukemias, and other malignancies. As a result, a safer yet equally effective alternative therapy is necessary. MMF is a relatively specific inhibitor of lymphocyte proliferation that has been found to minimize the incidence of acute rejection in renal transplant patients.[16,17,13,14] In murine models of lupus nephritis, MMF attenuates the severity of kidney disease and significantly prolongs survival.[15] Early observational studies revealed that these medicines might be effective in causing remission of lupus nephritis. MMF both safe and effective in the treatment of lupus nephritis patients.[18]

In the present result, there was a significant differentiation ($P< 0.05$) between before and after laboratory analysis for the two treatments. With tend toward a decrease in Hb; sCr; Alb/Cr ratio and ESR tested the treatment of the patient in GP1 with iv CYC by -14.2; -30.6; -72.1 and -56%. On the other hand, an increase in sAlb value by 24% was noticed. On the other hand, Hb; sCr; Alb/Cr ratio, and ESR in GP2 treated with MMF tend to decrease by -13; -27.5; -80.6, and -45.8% respectively. While an increase in sAlb value by 22% has been observed.

In comparison between groups sAlb, sCr, and Alb/Cr ratio show a decrease in MMF which was reported from ivCYC by -2.8; -8.3, and -26% respectively. On the other hand. an increase in Hb and ESR in the MMF group which was reported from the ivCYC group by 4 and 29% respectively. Rather than there was no significant differentiation ($P> 0.05$) between the patients treated with iv CYC or MMF.

There were no significant changes in laboratory-tested analyses between the two groups, according to the current findings. **Gadakchi et al.,**[19] and **Mak and colleagues**[18] found similar results to ours. **Appel and colleagues** [20] reported in another trial that therapy with MMF and CYC was effective in 56% and 53% of patients, respectively, and concluded that both medications had the same efficacy in producing remission in lupus nephritis, which was consistent with the current study.

Similarly, the current results found no significant difference in the recorded rate between both treatment groups, which is consistent with what has been reported by **Sogayise et al.** [21]

Our findings are congruent with those of **Sahay et al.**[22], who examined the efficacy of three LN therapy regimens (ELNT, NIH, and MMF). The European Lupus Nephritis Trial (ELNT) regimen included six 500 mg IV CYC doses given biweekly, but the National Institute of Health (NIH) regimen included 0.5 g/m^2 monthly treatment for six months, with MMF given at a dosage of 1200 mg/m^2. They concluded that for the treatment of LN, both MMF and CYC-based regimens are successful and that there was no noticeable difference in improvement between the groups investigated.

5. CONCLUSIONS

This study found that both oral mycophenolate mofetil and cyclophosphamide had beneficial benefits in the treatment of lupus nephritis.

Supplementary Materials: Supplementary file 1.

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Conflicts of Interest: Author(s) disclose no potential conflicts of interest.

Ethical Statement: Written informed consent was obtained from all patients in our study. All information was taken in secret and was used secret codes for each patient. The study was approved by the Ethics committee of the Faculty of Medicine, Al-Azhar University under the number 0000085.

Author Contribution: All authors shared the study design, data collection and literature research, SD and MA were responsible for data analysis, patient sampling, and doing an investigation, HA critically

reviewed the paper and has a main role in the revision of the final manuscript, All authors read and approved the final manuscript.

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