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Efficacy of Cyclophosphamide and Mycophenolate Mofetil Based Induction Therapy in Egyptian Patients with Systemic Lupus Erythematosus-associated Nephritis

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Abstract

Background: Lupus nephritis (LN) is a serious manifestation of systemic lupus erythematosus. Induction immunosuppression can include high dose cyclophosphamide (NIH protocol), low dose cyclophosphamide (Euro-lupus protocol) or mycophenolate mofetil (MMF). We aimed to assess the efficacy and safety of the 3 induction regimens in Egyptian patients with LN.

Patients and methods: A cohort of 90 patients with LN was divided into 3 groups according to their treatment regimen: NIH protocol, Euro-lupus protocol, and MMF-based therapy groups. Therapy response was assessed at 6 months and was divided into either: complete remission (CR), partial remission (PR), or lack of response.

Results: MMF-based therapy achieved significantly higher complete remission rate (74.3% vs. 51.7% in NIH, 42.3% in Euro-lupus groups; p=0.03). There was no significant difference between the 3 groups in overall remission (65.5 % in NIH, 69.3% in Euro-lupus, 85.7% in the MMF groups; p=0.14), or in partial remission. The six-month survival did not differ between the 3 groups (93.1% in NIH, 96.2% in Euro-lupus and 100% in MMF groups; p=0.3). Infection rates were highest among the NIH followed by Euro-Lupus and then MMF groups (p<0.05). Diarrhea was more common among the MMF group (p=0.02).

Conclusion: MMF can be prescribed as a first line therapeutic option in Egyptian patients with lupus nephritis, while considering low dose cyclophosphamide therapy as an alternative option. Our study is the first Egyptian study to demonstrate a head-to-head comparison between the 3 most commonly used induction regimens for lupus nephritis patients.

Keywords: Lupus nephritis, Systemic lupus erythematosus, Induction therapy, Cyclophosphamide, Mycophenolatemofetil.

1. INTRODUCTION:

Lupus nephritis (LN) is one of the serious manifestations of systemic lupus erythematosus (SLE), which occurs in approximately 50% of patients, with a predilection for certain ethnic groups such as Afro-Americans (70%) **[1].** The development of LN adversely affects prognosis in patients with SLE, with higher mortality rates than in patients who do not develop nephritis and up to 10% developing end stage renal disease **[2]**. Management of LN requires a timely and judicious use of immunosuppressive therapy in order to achieve the best possible clinical efficacy while exposing the patient to the minimal drug-related toxic effects**[3].**

Multiple intense immunosuppressive regimens have thus been developed to induce disease remission **[4].** These include, besides steroids, either high dose cyclophosphamide: the National Institute of Health (NIH) protocol **[5],** low dose cyclophosphamide: the Euro-Lupus Nephritis Trial (ELNT) protocol **[6]** or mycophenolate mofetil (MMF) **[7-9].** The later two regimens have proven comparable efficacy and less toxicity than exposure to high dose cyclophosphamide **[6, 7],** and thus represented reasonable alternatives. The high dose cyclophosphamide regimen can then be reserved for patients at high risk for renal failure **[10].**

However, the disease activity and response to therapy vary among different ethnic groups **[11].** In the Aspreva lupus management study for example, despite an overall similar renal response to MMF and high dose CYC, such response was not uniform across all represented ethnic groups. While response rates were similar for Asian and white patients, intravenous (IV) cyclophosphamide was less effective in patients of African or Hispanic descent **[7].** In the ELNT study on the other hand, few black or African Caribbean patients were included. Thus, caution should be exercised in extrapolating the results of the ELNT to other lupus nephritis populations with different ethnic backgrounds **[6].**

Therefore, we aimed to assess the efficacy and safety of the three remission-inducing regimens in Egyptian patients with LN at our center.

2. SUBJECTS AND METHODS:

We studied a cohort of 90 adult patients with proliferative LN who were followed up at the Rheumatology Department of Zagazig University hospitals in Egypt. Patients of either sex between the ages of 18 and 60, diagnosed to have SLE as per the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [12], and biopsy-proven class III, IV, III+V, or IV+V LN based on the International Society of Nephrology/Renal Pathology Society classification **[13]** were included. Patients with crescentic lupus nephritis were excluded.

Patients' demographics, biopsy findings, baseline and 6-month laboratory parameters including creatinine levels, urinary protein excretion rates, complete blood picture, immunological parameters (ANA at baseline and C3 and C4 levels and anti-ds-DNA titers) were reported. eGFR was assessed using the Modification of Diet in Renal Disease (MDRD) study equation **[14].**

Immunosuppressive protocols and drug dosing:

Patients were treated by the attending physician according to the American College of Rheumatology guidelines **[15].** As induction therapy, patients received either: (1) high dose cyclophosphamide (NIH protocol) (500–1000 mg/m2 i.v. once a month for 6 doses), (2) low dose cyclophosphamide (Euro-lupus protocol) (500 mg i.v. once every 2 weeks for a total of 6 doses), or (3) MMF-based regimen (1 gm bd with a target of 1.5 gm bd if tolerated). All patients were treated with intravenous methylprednisolone (0.5–1 g/day for three doses) followed by oral prednisolone at a dose of 1 mg/kg/day for four to eight weeks, and then the dose was tapered gradually to reach 5 to 10 mg/day by the end of four to six months guided by the patient response. This was followed by maintenance therapy with daily oral azathioprine (AZA) (2 mg/kg) or daily oral MMF (1.0–2.0 g/day). All subjects were given hydroxychloroquine (200-400 mg/day) as well as either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Monitoring response to therapy:

Therapy response was assessed at 6 months and was divided into either: complete remission (CR), partial remission (PR), or lack of response. CR was defined as a urinary protein-creatinine ratio (uPCR) < 500 mg protein/gm creatinine (roughly equivalent to proteinuria < 0.5 g/24 h) and a normal or near-normal GFR (within 10% of the patient's normal GFR if previously abnormal). PR was defined as normal or near-normal GFR with a ≥ 50% reduction in proteinuria to subnephrotic levels **[16, 17].** Non-responders were those who failed to achieve either CR or PR and thus required changing to an alternative immunosuppressive regimen.

Ethical approval:

The study was approved by the Institutional Review Board of Zagazig Faculty of Medicine and carried out according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical analysis:

The data were analyzed by Statistical Package for Social Science (Version 20.0. Armonk, NY: IBM Corp). Qualitative variables were expressed as numbers and percentages. Quantitative data were represented as mean±SD. Data comparison between the 3 groups was done by one-way analysis of variance for parametric variables and Kruskal–Wallis test for non-parametric variables. Pearson's Chi-square ($\chi 2$) test was used to compare qualitative data, therapy outcomes as well as the side effects between the three groups. A P-value <0.05 was considered statistically significant.

3. RESULTS

The study included 90 SLE patients, with the mean age 30 ±7 years; 80 of them were females. Overall, LN grade IV was the commonest biopsy finding followed by class III (38/90 (42.2%) and 26/90 (28. 8%) respectively). The rest of patients had class V LN with a proliferative activity of either class III or IV.

Patients were divided into 3 groups according to the treatment regimen received: NIH, Euro-lupus, and MMF-based therapy groups. The 3 groups were similar in age, gender, LN class distribution, activity and chronicity indices, as well as in baseline laboratory criteria **(Table 1).**

When we assessed the response to therapy, there was no significant difference between the 3 groups in the overall remission rates (65.5 % in NIH group vs. 69.3% in Euro-lupus vs. 85.7% in the MMF group; p=0.14), as well as in the partial remission rates. However, the

MMF-based therapy achieved significantly higher complete remission rate than the other 2 groups (p=0.03) **(Table 2).** The six-month survival rates also did not differ between the 3 groups (93.1% in the NIH group, 96.2% in the Euro-lupus group and 100% in the MMF group; p=0.3) **(Figure 1).**

We then considered the adverse events in each group and found significantly higher rates of infection and amenorrhea among the NIH group followed by the Euro-Lupus and then the MMF groups (p<0.05). In contrast, diarrhea was significantly higher among the MMF group than the other 2 groups (p=0.02) **(Table 3).**

Table (1): Baseline characteristics of the study population

Variables	**NIH regimen (n=29)**	**Euro-lupus regimen (n=26)**	**MMF-based therapy (n=35)**	**p-value**
Age	29.1±7.3	30.7±4.2	31.5±4.6	0.2*
Gender (female/male)	25/4	24/2	31/4	0.77^
Biopsy class III 26 (28.9%) IV 38(42.2%) III+ V 12 (13.3%) IV+V 14(15.6%)	 12 (41.4%) 9 (31.0%) 5 (17.2%) 3 (10.3%)	 6 (23.1%) 11 (42.3%) 3 (11.5%) 6 (23.1%)	 8 (22.9%) 18 (51.4%) 4 (11.4%) 5 (14.3%)	0.4^
Activity index (out of 24)	13.45±3.06	13.15±3.9	12.23±3.05	0.3*
Chronicity index (out of 12)	3.74±2.09	3.86±1.93	3.59±2.13	0.8**
Serum creatinine	1.6±1.24	1.7±1.15	1.5±1.21	0.8**
eGFR(ml/min/1.73m3)	63.7±34	57.4±26	60.2±31	0.7**
uPCR	2.57±1.9	2.73±1.4	2.91±1.3	0.6**
Hemoglobin	11.3±1.8	11.4±2.1	11.7±0.7	0.6
WBCs (×1000)	6.6±3.3	5.6±2.3	7.2±3.7	0.1**
Platelets (×1000)	282.3±117.1	291.8±115.9	292.4±108.1	0.9**
Low C3	20 (69.0%)	18 (69.2%)	24 (68.6%)	1^
Low C4	18 (62.1%)	17 (65.4%)	21 (60.0%)	0.9^
Anti-ds-DNA	26 (89.7%)	19 (73.1%)	26 (74.3%)	0.2^

eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; NIH, National Institute of Health; uPCR, urinary protein creatinine ratio; WBCs, white blood cells
*ANOVA(F-test), **Kruskal-Wallis test, ^Chi-Square test.

Table 2:Renal response at 6 months of therapy

Variables	**NIH regimen (n=29)**	**Euro-lupus regimen (n=26)**	**MMF-based therapy (n=35)**	**p-value***
Overall remission	19 (65.5%)	18 (69.3%)	30 (85.7%)	0.14
Complete remission	15 (51.7%)	11 (42.3%)	26 (74.3%)	0.03
Partial remission	4 (13.8%)	7 (26.9%)	4 (11.4%)	0.2
Non-responders	7 (24.1%)	6 (23.1%)	4 (11.4%)	0.3
ESRD	1 (3.44%)	1 (3.8%)	1 (3.44%)	0.9
Death	2 (6.89%)	1 (7.7%)	0 (0.0%)	0.3

MMF, mycophenolate mofetil; NIH, National Institute of Health
*Chi-Square test

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Table 3: Adverse events in different treatment groups.

Variables	NIH regimen (n=29)	Euro-lupus regimen (n=26)	MMF-based therapy (n=35)	p-value
Anemia	4 (13.8%)	1 (3.8%)	2 (5.7%)	0.3
Infections	9 (31.1%)	5 (19.2%)	2 (5.7%)	0.03
Leucopenia	2 (6.9%)	1 (3.8%)	1 (2.8%)	0.7
Pancytopenia	3 (10.3%)	1 (3.8%)	2 (5.7%)	0.6
Diarrhea	3 (10.3%)	2 (7.7%)	10 (28.6%)	0.02
Amenorrhea	8 (27.6%)	2 (7.7%)	1 (2.8%)	0.007

MMF, mycophenolate mofetil; NIH, National Institute of Health

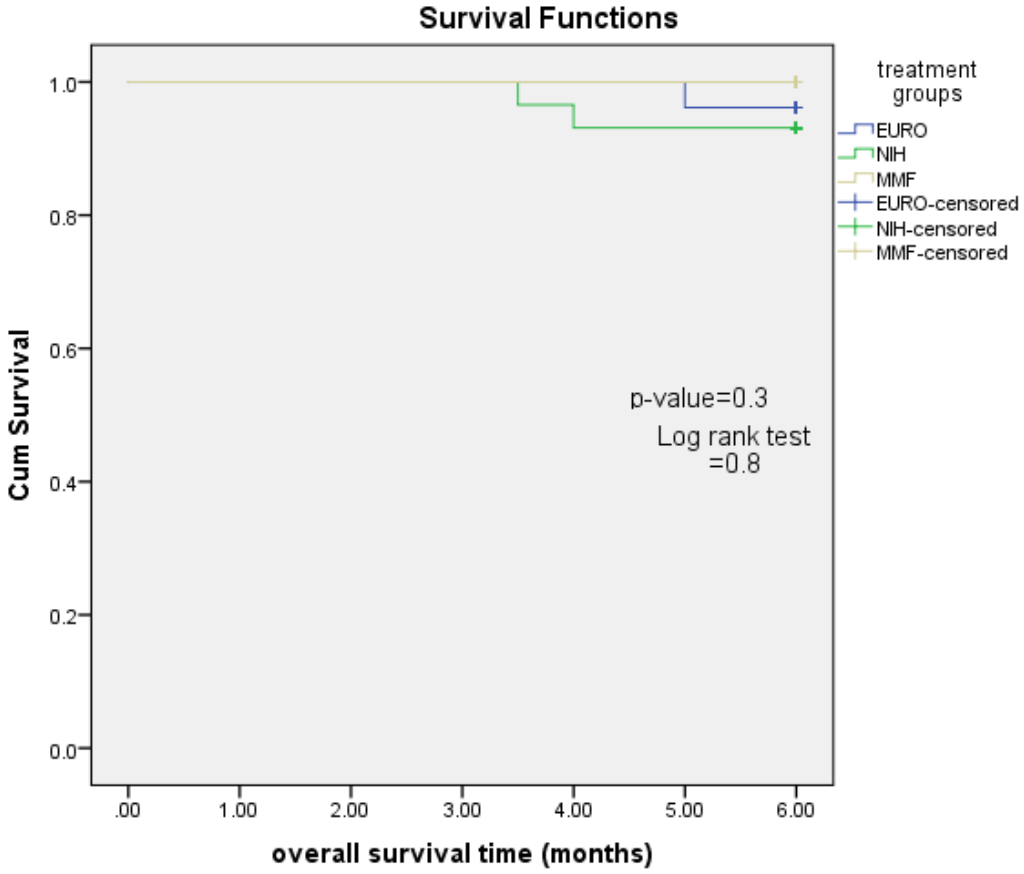

Figure 1: Kaplan–Meier patient survival analysis among the three groups after 6 months.

4. DISCUSSION:

Lupus Nephritis has a potentially serious impact on both kidney function and patient survival. The disease severity and response to therapy vary depending on multiple factors including patient ethnicity **[7, 11].** It is thus vital to assess the therapy response among different ethnic groups. However, evidence from studies involving Egyptian lupus patients is yet sparse and discordant. In our study, we treated a cohort of patients with biopsy-proven LN with either: high dose cyclophosphamide, low dose cyclophosphamide or MMF-based treatment regimens. Overall remission rate as well as kidney and patient survival were similar amongst the three treatment regimens. However, MMF-based therapy achieved higher rate of complete remission than the other two protocols.

Overall, our results showed remission in over two thirds of patients. We then stratified the response according to the induction protocol. The MMF-based therapy could achieve significantly higher rate of complete remission than patients prescribed high or low dose cyclophosphamide. However, partial remission rates were comparable between the 3 groups. The overall remission rates were also similar; yet numerically higher with the MMF-based regimen. In the Aspreva study comparing MMF to cyclophosphamide-based therapies, remission rates were similar between both groups, yet MMF was superior in Hispanics upon post hoc analysis **[7].** Similar result was obtained in Egyptian lupus patients when MMF and high dose cyclophosphamide were found to have comparable efficacy in one study **[18],** and subsequently in another study (overall remission: 69.5% (25/36) and 75.7% (25/33) respectively; p=0.55) **[19].** In contrast, an earlier multicenter randomized controlled trial showed that MMF was more effective than IV cyclophosphamide in inducing remission of lupus nephritis **[8].** Similar response was shown in a recent large Egyptian retrospective study **[20].**

Comparing low dose IV cyclophosphamide to the high dose regimen, European SLE patients had similar renal remission rates (71% vs 54%; p>0.05) in the ELNT study **[6],** and similarly, the Egyptian patients in another study **[21].** When low dose cyclophosphamide was compared to MMF-based therapy in an Indian study, both were equally effective and low dose cyclophosphamide could be considered a good treatment option for induction given its fewer side effects, thus tolerability, and lower cost **[22],** which is of particular relevance in resource-limited settings.

The decision on the induction regimen should also consider the side effect profile of each therapy. In our study, a higher rate of infections was observed with the cyclophosphamide-based therapies, more with high dose, compared to more diarrheal episodes with the MMF-based therapies. A higher rate of infections with the high dose cyclophosphamide therapy was consistently observed among previous studies, whether compared to low dose cyclophosphamide **[6]** or MMF **[8].** Yet, there was no significant difference in patient or renal survival between the study groups. Amenorrhea was another side effect observed at higher frequency with the high dose cyclophosphamide. However, no such difference was evident in previous studies comparing low and high dose cyclophosphamide **[6]** or low dose cyclophosphamide and MMF **[22].** However, it is worth noting that in our patients, there is tendency to prescribe MMF-based therapy. This is understandable considering the potential impact of cyclophosphamide on fertility in ladies of the childbearing age **[19].** A cost difference between cyclophosphamide and MMF should be also considered, where the cumulative cost of MMF therapy can almost be seven times that of 3-month CYC and 3 months of azathioprine therapy **[22].**

Our study has some limitations, in particular the small population size and its single center nature. However, it is the first Egyptian study to demonstrate a head-to-head comparison between the 3 most commonly used induction regimens for lupus nephritis patients.

5. CONCLUSION:

our results suggest that MMF can be prescribed as a first line therapeutic option in Egyptian patients with lupus nephritis, while considering low dose cyclophosphamide therapy as an alternative option. Large dose cyclophosphamide should be better reserved for patients with the severe forms of the disease.

Declarations:

Funding: the authors received no funds.

Conflicts of interest: the authors have no conflict of interest.

Ethics approval: The study was approved by the Institutional Review Board of Zagazig Faculty of Medicine and carried out according to the Declaration of Helsinki.

Consent to participate: all participants provided written informed consent

Consent for publication: all authors consent for manuscript submission.

Availability of data and material: The datasets analysed during the current study are not publicly available to protect patients' privacy but are available from the corresponding author on reasonable request

Authors' contributions: All authors contributed to the manuscript in significant ways. All authors contributed to the study design, Dr.Hala A Gaballah and Dr.Shimaa M Abd El-Wahab contributed to the study conception, analyzed the data and contributed to writing the article. In addition, Dr.RehamAbd-Elkhalek, Dr. Ola A Hussein and Dr Marwa M El-Mosely collected the samples and data and participated in data analysis. All authors contributed to drafting the paper, its critical revision and approved the final version.

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