Comparison between high-dose, low-dose cyclophosphamide and mycophenolate mofetil in treatment of proliferative lupus nephritis (an Egyptian multicenter retrospective study)

Rasha A. Abdel Noor[a], Mervat Eissa[b], Hanaa I. Okda[c], Hend H. Abdelnabi[d], Sahar A. Ahmed[e], Eman F. Mohammed[f], Noha Abdel Salam[g], Enas S. Zahran[h]

[a]Rheumatology Unit, Department of Internal Medicine, [c]Nephrology Unit, Department of Internal Medicine, [d]Nephrology Unit, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, [b]Rheumatology Department, [e]Rheumatology & Immunology Unit, Department of Internal Medicine, Faculty of Medicine, Cairo University, [f]Rheumatology & Immunology Unit, Department of Internal Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, [g]Rheumatology and Immunology Unit, Department of Internal Medicine, Faculty of Medicine, Mansoura University, Mansoura, [h]Rheumatology & Immunology Unit, Department of Internal Medicine, Faculty of Medicine, Menoufia University, Shebin El Kom, Egypt

Correspondence to Rasha A. Abdel Noor, MD, Department of Internal Medicine & Rheumatology, Faculty of Medicine, Tanta University, Elgish Street, Tanta, Gharbia, 31111, Egypt.
e-mails: rashaabdelnoor@yahoo.com, rashaabdelnoor@med.tanta.edu.eg

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Background
Proliferative lupus nephritis (LN) is an aggressive pathological lesion of LN. Corticosteroids, cyclophosphamide (CYC) pulse therapy either by high dose; National Institute of Health (NIH) CYC or low dose; European cyclophosphamide regimen (EURO-CYC), and mycophenolate mofetil (MMF) are the best valid lines for treatment, but the choice between them is still challenging. The objective of this study was to compare the efficacy of both CYC regimens and MMF in the treatment of proliferative LN patients.

Patients and methods
We retrospectively collected the data of 225 biopsy-proven proliferative LN patients (adults and juveniles) from five tertiary centers. Forty four of patients received low-dose regimen, 124 received high-dose regimen, and 57 received MMF. All demographic data, laboratory tests, activity markers, and systemic lupus disease-activity index were recorded and compared at initial presentation and at 3, 6, 12, and 24 months of follow-up.

Results
After 6 months of treatment, 61.2% of NIH-CYC group reached complete response, while the rate was 40.9% of EURO-CYC group and 52.7% for MMF group, and the results were in favor for the NIH group over EURO group, while there was no difference between NIH and MMF groups, but at the end of 12th, 18th, and 24th months of follow-up, the outcomes of the three groups were comparable in efficacy and safety.

Conclusion
For induction treatment of proliferative LN, high-dose CYC shows a better and rapid complete response after the sixth month of treatment in adults and juvenile LN patients, but after the first year of therapy, the three regimens have comparable efficacy and safety.

Keywords:
cyclophosphamide, lupus nephritis treatment, mycophenolate mofetil, proliferative lupus nephritis, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem disease, renal involvement occurs in ~40–75% of patients [1]. Severe proliferative lupus nephritis (LN) is associated with poor renal outcomes and requires aggressive therapy [2]. Management of LN consists of induction therapy to achieve remission and long-term maintenance therapy to prevent relapse [3]. Treatment options include glucocorticoids and immunosuppressive agents, such as cyclophosphamide (CYC), mycophenolate mofetil (MMF), azathioprine, and calcineurin inhibitors. These drugs have considerable toxicity and are not effective in all patients [4].

The use of intravenous CYC is based on studies in the 1970s and 1980s at the National Institutes of Health (NIH) [5]. The standard treatment is the NIH protocol, which consists of intravenous CYC (0.5–1 g/m^2, adjusted to white blood cell nadir), given monthly for the first 6 months and then quarterly for at least 12 months [2]. The response is often slow and is associated with increased risks for adverse effects [6]. Several alternative treatments

have emerged, including the European (EURO) Lupus Nephritis Trial (ELNT) protocol, which seems to be as effective. It comprises six pulses of a low fixed dose of 500 mg given every 2 weeks for six doses followed by azathioprine as a remission-maintenance agent [7].

MMF was at least as effective as intravenous CYC in induction treatment in previous trials [8–11]. Meta-analyses of these and smaller trials suggested that MMF may offer advantages over intravenous CYC [12] and fewer side effects [13,14].

In this study, we will assess the efficacy and safety of different immunosuppressive regimens for the treatment of Egyptian proliferative LN patients.

Objectives: To compare the response to treatment and disease outcomes between high-dose, low-dose CYC regimens and MMF in the treatment of proliferative LN patients.

Patients and methods

Study design and data collection: This is an Egyptian multicenter retrospective cohort study. Data were collected from files of 1136 adult SLE (a-SLE) and juvenile SLE (j-SLE) patients between 2010 and 2020 from five Egyptian tertiary rheumatology and nephrology centers.

Patients in this study were diagnosed according to either the 1997 Modified American College of Rheumatology Criteria for the classification of SLE [15] or Systemic Lupus International Collaborative Clinics criteria for SLE [16]. Inclusion criteria were proliferative LN patient classes III and IV isolated or combined with other classes classified according to the International Society of Nephrology & Renal Pathology Society classification of renal biopsy [17], all patients were under immunosuppressive treatment and follow-up for at least 1-year duration. The patients were excluded from the study if their disease duration was less than 12 months or if they were on irregular courses of immunosuppressive regimens, also patients with overlap with other connective-tissue diseases, diabetes mellitus, or pregnancy were excluded from the study.

By reviewing the files of all patients, demographic and clinical manifestations occurring at the initial presentation of the disease, laboratory, serological, and therapeutic regimens of the patients collected from the files of all patients.

Laboratory data: Complete blood picture, urea, creatinine, 24-h urinary proteins, complement 3 (C3), complement 4 (C4), and systemic lupus disease-activity index (SLEDAI) [18], all were recorded at initial presentation of and at follow-up at 3, 6, 12, and 24 months.

Serologic tests: Autoantibody assays (antinuclear antibodies, anti-double-stranded antibody, anticardiolipin, and lupus anticoagulant).

Renal biopsy: Findings of renal biopsy done at initial presentation of LN were recorded. LN was staged according to the classification revised by the International Society of Nephrology and the Renal Pathology Society in 2003.

Treatment regimens that were used for induction and maintenance of LN and their complications (if any) were recorded at initial treatment and during follow-up (at 3, 6, 12, and 24 months) after initial treatment. According to the regimen used, the patients were classified into three groups:

Group 1: patients who received low-dose CYC EURO-Lupus nephritis protocol (EURO-CYC) that means 500 mg of intravenous CYC every other week with a minimum of six doses.
Group 2: patients who received high-dose NIH-CYC that means intravenous CYC (0.5–1 g/m^2) given monthly for 6 months.
Group 3: patients who received MMF at a dose of 2–3 g per day.

All patient groups were on prednisolone therapy starting by pulse methylprednisolone in most of the cases followed by 1 mg/kg for 1 day and the dose was gradually tapered according to disease activity and physician opinion. Also, they received oral hydroxychloroquine and additive therapies like angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, other antihypertensives, prophylactic oral calcium, and vitamin D.

The study endpoints (treatment response) were defined as follows:

The primary outcome 'primary endpoint' 'partial response' (PR) is defined as

(1) A reduction in the urinary total 24-h protein (UTP) to less than 3.5 g in patients with baseline nephrotic-range proteinuria (UTP ≥3.5 g).

(2) A reduction in the UTP by more than 50% in patients with subnephrotic proteinuria (UTP <3.5 g).
(3) Stabilization (±25%) or reduction of serum creatinine and rise of estimated glomerular-filtration rate from the baseline value.

The secondary outcome 'second endpoint' 'complete response' (CR) is defined as

(1) Return of serum creatinine to the previous baseline.
(2) Plus a decline in the UTP to less than 500 mg.

No response (NR): No improvement as regards proteinuria or renal-function tests as primary or secondary endpoints.

Ethics: This study was in agreement with the ethical guidelines of the Declaration of Helsinki and was approved by the ethical committee of the contributing centers after providing written informed consents from participant individuals.

Statistical analysis

Analysis of data between the three studied groups was performed with SPSS statistical software, version 21. Data presented as mean±SD and percentage, analysis of variance, post hoc (Tukey test), and *t* test were used for the comparison of continuous parametric data, while the χ^2 test was used for nonparametric data. Paired *t* test was used to compare the one-group data during follow-up. *P* value less than 0.05 was considered statistically significant.

Results

Data were collected from files of 1136 Egyptian lupus patients (a-SLE and j-SLE) aged 10–56 years, 529 (46.6%) with LN. Only 235 patients who had proliferative LN classes (III, IV, III–IV, III–V, and IV–V) (44.4%) were included in the study.

Then 10 cases with treatment shift were excluded from follow-up; therefore, the actual number of cases included in this study was 225 proliferative LN patients.

Initial characteristics of all studied patients

The demographic data of 225 Egyptian a-SLE and j-SLE, initial clinical manifestations, the initial laboratory findings, SLEDAI, pulse-steroid treatment, and renal biopsies are mentioned in detail in Table 1. The female/male ratio was 5.43/1, the mean age at diagnosis was 28.4 ±9.3 years, with disease duration 4.03±3.2 years, 44 patients were on EURO-CYC regimen, 124 patients were on NIH-CYC, and 57 patients were on MMF regimen. The most frequent initial manifestations in the three groups were constitutional, mucocutaneous, arthritis, and hematological manifestations. There were significantly high levels of proteinuria in the MMF group, pulse methylprednisolone was used more in EURO and NIH groups than in the MMF group. Renal biopsies were performed for all 225 patients. LN classes III and IV were the commonest findings in the three groups.

Follow-up after 3 and 6 months

There was a significant improvement in all activity scores in the three groups, but at the end of the third month, the improvement in C3 and C4 was more in the MMF group and SLEDAI was improved more in NIH-CYC and MMF groups and proteinuria markedly decreased with the NIH group. At the end of 6 months, similar results were detected, but C4 improved more with the MMF group (Table 2).

Follow-up at 12 months

Showed significant improvement of activity parameters in each group than the initial measures with noticed significant improvement in serum creatinine in the NIH-CYC group than the EURO-CYC group and more improvement in C4 level with MMF group than EURO-CYC group (Table 3).

Follow-up after 1 year of induction therapy

At 18th and 24th months, the total number of patients decreased to 120 and 69, respectively, their follow-up laboratory tests are shown in Tables 3 and 4 that show no significant difference between the three groups in any parameter.

The treatment response is summarized in Table 5, which shows no significant difference between EURO-CYC, NIH-CYC, or MMF regimens in outcomes at the end of the third month where 22.7% of patients had complete remission, 27.3% had partial remission, and 50% failed to reach remission in the EURO-CYC-regimen group, while the percentages were 34.7% CR, 30.6% PR, and 34.7% NR for the NIH-CYC-regimen group and 29.8% CR, 35.1% PR, and 35.1% NR for the MMF group, respectively. At the sixth month, the treatment-response rates increased in all groups to reach 40.9% CR, 31.8% PR, and 27.3% NR for the EURO-CYC group, 61.2% CR, 27.5% PR, and 11.3% NR for the INH-CYC group, and 52.7% CR, 36.8% PR, and 10.5% NR for the MMF group, and there was a significant difference between EURO and

Table 1 Demographic data & initial characteristics of all studied patients

	Group 1: EURO-CYC (*N*=44)	Group 2: NIH-CYC (*N*=124)	Group 3: MMF (*N*=57)	*P* value
Age (years) (mean±SD)	29.4±7.9	29.9±9.2	23.6±8.7	0.001*
Total (*N*=225)		*P*1=0.9, *P*2=0.004*, *P*3=0.001*		
28.4±9.3				
Sex [*n* (%)]				
F190 (84.4%)	35 (79.5)	105 (84.7)	49 (86)	0.6
M 35 (15.6%)	9 (20.5)	19 (15.3)	8 (14)	
F/M ratio (5.43 : 1)	3.88 : 1	5.53 : 1	6.13 : 1	
Duration of the disease (years) (mean±SD) 4.03 ±3.2	3.1±1.6	4.8±3.7	3.03±2.3	0.001*
Initial presentations [*n* (%)]				
Malar rash	34 (77.3)	82 (66.1)	43 (75.4)	0.2
Arthritis	33 (75)	73 (58.9)	34 (59.6)	0.1
Oral ulcers	28 (63.6)	79 (63.7)	33 (57.9)	0.7
Photosensitivity	24 (54.5)	73 (58.9)	33 (57.9)	0.8
Alopecia	25 (56.8)	66 (53.2)	22 (38.6)	0.1
Serositis	19 (43.1)	48 (38.7)	24 (42.1)	0.8
Leucopenia	10 (22.7)	37 (29.8)	16 (28.1)	0.6
Thrombocytopenia	8 (18.2)	36 (29)	10 (17.5)	0.1
Hemolytic anemia	14 (31.8)	30 (24.2)	3 (5.3)	0.002*
CNS involvement	6 (13.6)	22 (17.7)	10 (17.5)	0.8
Discoid lupus	6 (13.6)	17 (13.7)	9 (15.8)	0.1
Hb (g %) (mean±SD)	9.2±1.7	9.6±2.2	9.4±1.7	0.6
		*P*1=0.6, *P*2=0.8, *P*3=0.9		
WBCs $\times 10^3$	6.3±3.1	6.2±2.9	5.9±2.8	0.7
		*P*1=0.9, *P*2=0.7, *P*3=0.8		
Platelets $\times 10^3$	201.5±92.7	204.6±101.6	214.4±101.6	0.7
		*P*1=0.9, *P*2=0.7, *P*3=0.8		
Urea (mg %)	51.1±64.7	53.9±40.2	45.05±28.6	0.4
		*P*1=0.9, *P*2=0.7, *P*3=0.4		
Creatinine (mg %)	1.5±1.3	1.3±1.1	1.2±0.8	0.3
		*P*1=0.6, *P*2=0.3, *P*3=0.6		
C3 (mg %)	53.5±28.6	60.1±25.6	56.8±28.8	0.3
		*P*1=0.3, *P*2=0.8, *P*3=0.7		
C4 (mg %)	11.1±12.7	19.7±25.8	19.7±22.8	0.08
		*P*1=0.08, *P*2=0.1, *P*3=1		
Proteinuria (g/24 h)	2.8±1.7	2.3±1.7	3.5±2.4	0.001*
		*P*1=0.2, *P*2=0.1, *P*3=0.001*		
+ve ANA [*n* (%)]	44 (100)	124 (100)	54 (94.7)	0.001*
+ve Anti-dsDNA [*n* (%)]	44 (100)	113 (91.1)	52 (91.2)	0.1
+ve LAC [*n* (%)]	9 (20.5)	30 (24.2)	7 (12.3)	0.1
+ve ACL [*n* (%)]	8 (18.2)	37 (29.8)	8 (14)	0.2
SLEDAI (mean±SD)	18.1±6.4	16.6±7.06	16.9±5.3	0.4
		*P*1=0.3, *P*2=0.6, *P*3=0.9		
Pulse steroids therapy [*n* (%)]	44 (100)	122 (98.4)	43 (75.4)	0.001*
LN classes [*n* (%)]	Group 1 (*N*=44)	Group 2 (*N*=124)	Group 3 (*N*=57)	
Class III	13 (29.5)	69 (55.6)	27 (47.4)	
Class IV	29 (65.9)	47 (37.9)	29 (50.9)	
Class II and III	0	2 (1.6)	0	
Class III and IV	0	6 (4.8)	1 (1.7)	
Class IV and V	2 (4.5)	0	0	

ACL, anticardiolipin; ANA, antinuclear antibodies; Anti-dsDNA, anti-double-stranded antibody; C3, complement 3; C4, complement 4; EURO-CYC, European-cyclophosphamide regimen; LAC, lupus anticoagulant; LN, lupus nephritis; MMF, mycophenolate mofetil regimen; NIH-CYC, National Institute of Health cyclophosphamide regimen; SLEDAI, systemic lupus erythematosus activity index; WBC, white blood cell. *P* of analysis of variance (between groups), post-hoc *P*1 (between group 1 and 2), *P*2 (between group 1 and 3), *P*3 (between group 2 and 3). **P* value less than 0.05 is significant.

Table 2 laboratory data and disease activity after 3 and 6 months of different treatment regimens

Laboratory data and SLEDAI (mean ±SD)		Group 1: EURO-CYC (*N*=44)	Group 2: NIH-CYC (*N*=124)	Group 3: MMF (*N*=57)	*P* value
	Urea (mg %)	39.7±39.8	43.6±35.6 *P*1=0.7, *P*2=0.9, *P*3=0.5	37.8±22.1	0.5
	Creatinine (mg %)	1.9±2.3	1.3±1.3 *P*1=0.04*, *P*2=0.02*, *P*3=0.7	1.1±0.8	0.01*
After 3 months	C3 (mg %)	89.7±23.8	84.9±18.5 *P*1=0.3, *P*2=0.4, *P*3=0.01*	94.3±21.8	0.01*
	C4 (mg %)	24.08±21.06	23.4±24.8 *P*1=0.9, *P*2=0.006*, *P*3=0.001*	39.4±25.6	0.001*
	Proteinuria (g/24 h)	1.7±1.4	1.1±1.3 *P*1=0.04*, *P*2=0.1, *P*3=0.3	1.4±1.4	0.04*
	SLEDAI	7.8±5.03	5.8±3.9 *P*1=0.01*, *P*2=0.001*, *P*3=0.2	4.7±4.03	0.001*
	Urea (mg %)	36.3±23.5	36.5±23.2 *P*1=0.9, *P*2=0.9, *P*3=0.9	35.5±23.6	0.9
	Creatinine (mg %)	2.03±2.9	1.1±1.09 *P*1=0.007*, *P*2=0.9, *P*3=0.01*	1.1±0.9	0.005*
After 6 months	C3 (mg %)	102.7±18.9	101.08±20.3 *P*1=0.8, *P*2=0.8, *P*3=0.4	104.8±18.1	0.4
	C4 (mg %)	26.6±22.7	32.3±29.1 *P*1=0.4, *P*2=0.001*, *P*3=0.004*	46.4±25.8	0.001*
	Proteinuria (g/24 h)	1.3±1.4	0.8±1.3 *P*1=0.04*, *P*2=0.07, *P*3=0.9	0.7±0.8	0.04*
	SLEDAI	5.3±4.1	3.4±2.6 *P*1=0.004*, *P*2=0.01*, *P*3=0.9	3.8±3.6	0.003*

EURO-CYC, European-cyclophosphamide regimen; MMF, mycophenolate mofetil; NIH-CYC, National Institute of Health cyclophosphamide regimen; SLEDAI, systemic lupus disease activity index. *P* of analysis of variance (between groups), post-hoc *P*1 (between groups 1 and 2), *P*2 (between groups 1 and 3), *P*3 (between groups 2 and 3). **P* value less than 0.05 is significant.

NIH-CYC group with a more favorable outcome to the NIH group than EURO, while there was no difference between the NIH and MMF group.

After the sixth month, the patients were maintained on either azathioprine (1–2 mg/kg/day) 44.88% or MMF 1–2 g/d (40.44%), while 14.2% of patients who received NIH regimen continued to receive CYC every 3 months for 1 or 2 years and only one patient was maintained on methotrexate. We reported the outcomes of the 225 patients at 12 months and after that at 18th and 24th months. There was no significant difference between the three treatment regimens as regards treatment outcomes at the 12th, 18th, or 24th months of follow-up.

Treatment complications

Different types of complications were reported during the treatment, such as anemia, leukopenia, herpes zoster, urinary-tract infections, chest infection, gluteal abscess, etc., there was no difference between the three groups in the frequencies of complications as a whole, however, the frequency of hypertension was more in the EURO-CYC-regimen group, especially the initial 3 months, leukopenia and the need for dialysis were also found more in the EURO-CYC regimen (Fig. 1).

Discussion

Although there is an improvement in immunosuppressive regimens for LN over the last few decades, yet the choice of the best immunosuppressive line is still challenging. Corticosteroids, CYC-pulse therapy either by high dose or low dose, and MMF are the best valid immunosuppressive lines for the treatment of proliferative LN in the recent guidelines [19–22]. The NIH study recommends the use of steroid plus intravenous CYC in high dose monthly [5,23], due to the adverse effect of this regimen and the less-aggressive form of LN in the EURO population, the ELNT studied the use of a low fixed dose of pulse CYC (EURO regimen) [7]. Since that time, a lot of studies were done to compare the efficacy and safety of both regimens. Some results were favorable for ELNT and others were not. The MMF was added later to the two lines of treatment in all guidelines as an important drug for remission induction after the results of the Aspreva Lupus Management Study Group (ALMS) trial [11].

Table 3 Laboratory data and disease activity at 12th, 18th months of different treatment regimens

Laboratory data and disease activity at 12 months				
Laboratory data and SLEDAI (mean±SD)	Group 1 EURO-CYC (*N*=44)	Group 2 NIH-CYC (*N*=124)	Group 3 MMF (*N*=57)	*P* value
Urea (mg %)	37.6±38.5	33.4±18.2 *P*1=0.6, *P*2=0.9, *P*3=0.7	36.1±24.8	0.5
Creatinine (mg %)	1.7±2.2	1.1±0.9 *P*1=0.03*, *P*2=0.1, *P*3=0.9	1.1±1.1	0.03*
C3 (mg %)	105.5±18.9	105.5±19.9 *P*1=1, *P*2=0.9, *P*3=1	105.3±22.7	0.9
C4 (mg %)	31.09±20.4	37.7±30.6 *P*1=0.3, *P*2=0.02*, *P*3=0.1	46.2±25.7	0.02*
Proteinuria (g/24 h)	0.9±1.4	0.6±1.3 *P*1=0.1, *P*2=0.1, *P*3=0.9	0.5±0.8	0.1
SLEDAI	3.9±4.01	3.01±3.08 *P*1=0.2, *P*2=0.05, *P*3=0.4	2.4±4.9	0.06
Laboratory data and disease activity at 18 months				
Laboratory data and SLEDAI (mean±SD)	Group 1: EURO-CYC (*N*=21)	Group 2: NIH-CYC (*N*=71)	Group 3: MMF (*N*=28)	*P* value
Urea (mg %)	33.1±28	36.01±28.4 *P*1=0.9, *P*2=0.6, *P*3=0.6	41.5±38.4	0.5
Creatinine (mg %)	1.5±1.4	1.2±1.3 *P*1=0.6, *P*2=0.9, *P*3=0.7	1.4±1.6	0.5
C3 (mg %)	111±36.6	110±26.8 *P*1=0.9, *P*2=0.7, *P*3=0.7	105.04±20.3	0.6
C4 (mg %)	35.2±21. 6	35.4±29.3 *P*1=0.9, *P*2=0.4, *P*3=0.2	45±25.1	0.2
Proteinuria (g/24 h)	0.9±2.1	0.5±1.1 *P*1=0.9, *P*2=0.1, *P*3=0.9	0.3±0.3	0.08
SLEDAI	3.1±4.04	3.1±3.7 *P*1=0.9, *P*2=1, *P*3=0.9	3±4.1	0.9

EURO-CYC, European-cyclophosphamide regimen; MMF, mycophenolate mofetil; NIH-CYC, National Institute of Health cyclophosphamide regimen; SLEDAI, systemic lupus disease activity index. *P* of analysis of variance (between groups), post-hoc *P*1 (between groups 1 and 2), *P*2 (between groups 1 and 3), *P*3 (between groups 2 and 3). **P* value less than 0.05 is significant.

Table 4 Laboratory data and disease activity at 24th months of different treatment regimens

Laboratory data and disease activity at 24 months				
Laboratory data and SLEDAI (mean±SD)	Group 1: EURO-CYC (*N*=9)	Group 2: NIH-CYC (*N*=43)	Group 3: MMF (*N*=17)	*P* value
Urea (mg %)	22.3±3.6	34.5±20.2 *P*1=0.4, *P*2=0.06, *P*3=0.2	47.5±44.1	0.07
Creatinine (mg %)	0.9±0.3	1.08±0.6 *P*1=0.8, *P*2=0.4, *P*3=0.4	1.3±1.4	0.3
C3 (mg %)	116.4±17.1	112.7±19.4 *P*1=0.1, *P*2=0.9, *P*3=0.8	103.06±14.4	0.1
C4 (mg %)	50.2±24.7	39.2±34.3 *P*1=0.6, *P*2=0.8, *P*3=0.8	43.4±28.4	0.6
Proteinuria (g/24 h)	0.8±1.6	0.2±0.3 *P*1=0.08, *P*2=0.1, *P*3=0.9	0.3±0.3	0.1
SLEDAI	1.5±2.1	2.3±2.5 *P*1=0.6, *P*2=0.7, *P*3=1	2.3±3.01	0.7

EURO-CYC, European-cyclophosphamide regimen; MMF, mycophenolate mofetil; NIH-CYC, National Institute of Health cyclophosphamide regimen; SLEDAI, systemic lupus disease activity index. *P* of analysis of variance (between groups), post-hoc *P*1 (between groups 1 and 2), *P*2 (between groups 1 and 3), *P*3 (between groups 2 and 3).

In Egypt, LN occurs in more than a third of SLE cases, 33.1% in a recent Egyptian SLE cohort [24] and 43.7% in another one [25], proliferative LN is common in LN patients to represent almost 42.4% of LN cases [25]. There are no enough studies done to compare the three regimens together worldwide [26] or in our locality [27,28]. So, we performed this study to compare the efficacy of the three regimens in the treatment of Egyptian proliferative LN patients.

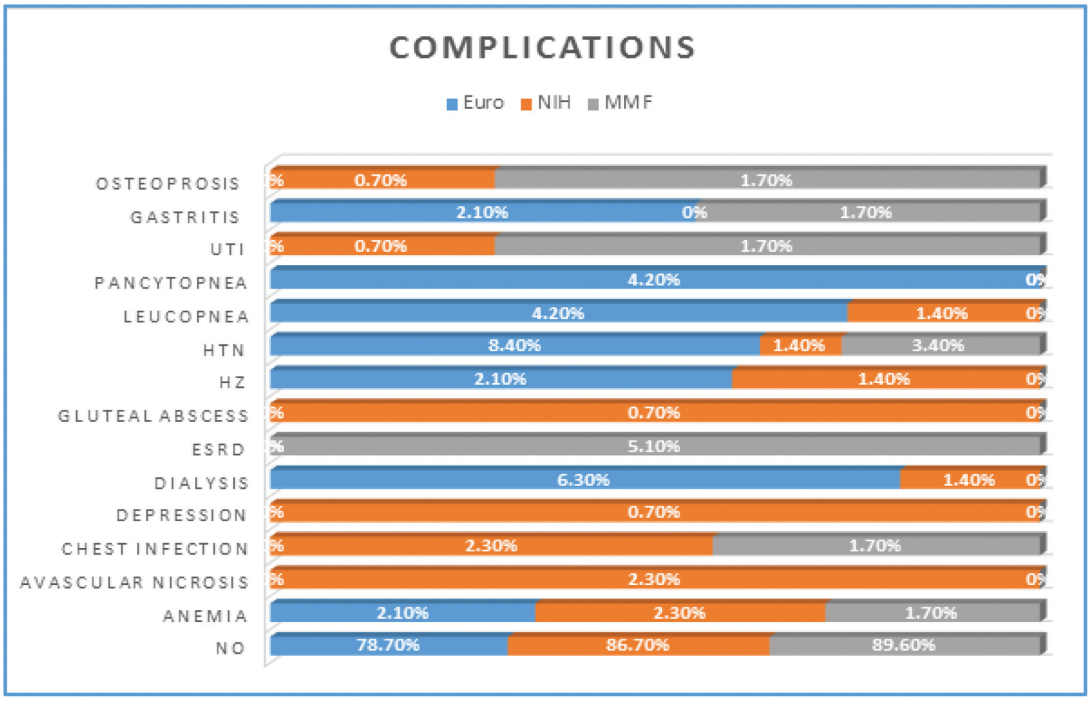
We retrospectively collected the data of 225 biopsy-proven proliferative LN patients. After 6 months of

Table 5 Primary and secondary end points (treatment response) of all studied groups

	Group 1: EURO-CYC (*N*=44)			Group 2: NIH-CYC (*N*=124)			Group 3: MMF (*N*=57)			
n (%)	PR	CR	NR	PR	CR	NR	PR	CR	NR	*P*
3 m	12 (27.3)	10 (22.7)	22 (50)	38 (30.6)	43 (34.7)	43 (34.7)	20 (35.1)	17 (29.8)	20 (35.1)	0.4
6 m	14 (31.8)	18 (40.9)	12 (27.3)	34 (27.5)	76 (61.2)	14 (11.3)	21 (36.8)	30 (52.7)	6 (10.5)	0.03*
				*P*1=0.01 *P*2=0.09 *P*3 =0.1						
				*P*1 (between groups 1 and 2), *P*2 (between groups 1 and 3), *P*3 (between groups 2 and 3)						
12 m	6 (13.7)	27 (61.3)	11 (25)	18 (14.5)	87 (70.1)	19 (15.3)	13 (22.8)	41 (71.9)	3 (5.3)	0.06
	Group 1: EURO-CYC (*N*=21)			Group 2: NIH-CYC (*N*=71)			Group 3: MMF (*N*=28)			
n (%)	PR	CR	NR	PR	CR	NR	PR	CR	NR	*P*
18 m	2 (9.5)	13 (61.9)	6 (28.6)	10 (14.1)	52 (73.2)	9 (12.6)	2 (7.1)	25 (89.2)	1 (3.5)	0.09
n (%)	Group 1: EURO-CYC (*N*=9)			Group 2: NIH-CYC (*N*=43)			Group 3: MMF (*N*=17)			
	PR	CR	NR	PR	CR	NR	PR	CR	NR	*P*
24 m	2 (22.2)	7 (87.8)	0	3 (6.9)	36 (83.7)	4 (9.3)	1 (5.9)	15 (88.2)	1 (5.9)	0.5

CR, complete response; EURO-CYC, European-cyclophosphamide regimen; MMF, mycophenolate mofetil; NIH-CYC, National Institute of Health cyclophosphamide regimen; NR, no response; PR, partial response. *P* of analysis of variance (between groups), post-hoc *P*1 (between groups 1 and 2), *P*2 (between groups 1 and 3), *P*3 (between groups 2 and 3). **P* value less than 0.05 is significant.

Figure 1



Treatment complications in the three treatment regimens.

treatment, 61.2% of the NIH-CYC group reached complete response, while the rate was 40.9% of the EURO-CYC group and 52.7% for the MMF group, and the statistical analysis was in favor for the NIH group over EURO, while there was no difference between the NIH and MMF group, but this difference disappeared at the end of the 12th month and the outcomes of the three groups were comparable and there were no differences between all regimens after the 18th month or 24th month of follow-up. Our results were similar to the ELNT study in some points where both high-dose and low-dose CYC produce the same renal remission at the end of the first year, however, in the ELNT trial, the rate of complete remission was higher for the EURO-CYC regimen (71%) than our study, also, the NIH-CYC regimen was not superior to the EURO-CYC regimen after six months, such differences may be explained by less severity of LN in EURO ethnicity [7]. Similar results were reported also by the Puerto Rican LN cohort that also retrospectively compared low-dose and high-dose CYC in 49 patients and concluded that the high-dose CYC therapy is more effective than the low-dose regime [29].

Other researchers compare both CYC doses like Sabry *et al.* [27], who reported no difference either in patients or in renal survival in both groups.

As regards MMF and CYC, many studies were done to compare the efficacy of both drugs as ALMS trial that found MMF more effective than intravenous NIH-CYC with a remission rate of 22.5% in MMF and 5.8% in NIH-CYC [11]. This study was criticized by many researchers as it was funded by a pharmaceutical company and also because its results had different outcomes than similar studies done on CYC [30].

So, another study funded by the same group (ALMS) was done in 2009 by Appel *et al.* [31] and they compared also MMF and high-dose CYC in 370 LN patients from classes III to V in an open-labeled clinical trial over 24 weeks and they did not detect any significant difference in response rate between the two groups. These results are similar to our results with the primary-efficacy endpoint (63.7%) for the MMF group compared with 57.1 for the IVC group, however, at the end of the 24th week. Only 8.6% patients in the MMF group and 8.1% in the IVC group achieved complete remission and this may be due to the difference in endpoint definitions.

Another Korean study was done recently on 39 patients with classes III and IV LN who received MMF or intravenous CYC as LN-induction therapy, and they retrospectively found that the efficacy does not differ between the two regimens [32]. Also, the other two studies, one Indian and one Nepalese, tested the INH-CYC regimen with MMF but in low dose from 1.5 to 2 g/day and both reported the comparable efficacy of both regimens in the treatment of proliferative LN [33,34]. Low-dose MMF 2 g/d was tested also in a recent AURA trial [35] in addition to voclosporin, a novel calcineurin inhibitor, the results of this study after 24 weeks were very promising to voclosporin and low-dose MMF. Despite there are many researches comparing the efficacy of MMF and high-dose CYC [11,31–38], there are few studies that compare the low-dose EURO-CYC regimen with MMF as an Indian-randomized trial done on 100 proliferative LN patients where there was no difference also between both drugs but better gastrointestinal tolerability and lower duration and cost in CYC-treated patients [39].

Although there are few studies comparing the three regimens for treatment of proliferative LN simultaneously, an important meta-analysis of 11 randomized clinical trials (1212 patients) was done and published in 2018 and they concluded that MMF and EURO-CYC regimens showed similar overall response rates with higher efficacy of both regimens than the NIH-CYC regimen [26]. Similar findings in a Japanese study where the renal response to different induction therapies such as NIH-CYC, the EURO-CYC, tacrolimus, and MMF was assessed in 64 Japanese patients with LN class III or IV and they reported no significant differences of cumulative CR rates and relapse-free survival for 3 years among the four different therapeutic regimens [40]. Also, in an Indian study, 144 patients with proliferative LN were randomly selected and the same efficacy among the three regimens for induction therapy was reported [41].

The present study compares the CYC and MMF not only in adult LN but also in juvenile-lupus patients (j-SLE) as we tested 32 j-SLE patients with proliferative LN, 20 of them were on MMF, 11 on NIH-CYC, while only one received EURO-CYC regimen, and we found that all of NIH-CYC (100%) and 95% of MMF patients responded to treatment, while the child who received EURO-CYC did not respond well to treatment and there was no significant difference between MMF and NIH-CYC regimens.

By comparing our results, Smith *et al.* [42] found that there was no difference between MMF and intravenous CYC in the treatment of proliferative j-LN. On the contrary, MMF was better in treating the j-LN patient as reported by Lau *et al.* [43], however, they conducted their retrospective study over 13 American j-LN patients only.

For the safety of the drugs, we reported some complications during the induction treatment, but there were no significant differences between CYC by its two doses or MMF. These results are reported by many authors [7,27–29,31–33,38,39,41,44], while others reported less alopecia, amenorrhea [37,45], leukopenia, anemia [40] infections [34], and more diarrhea with MMF [11,28,39] and some noticed more infection with high-dose CYC [11,26].

Although our study is a retrospective one and the numbers of patients are not equal in all groups, however, the total number of patients are more than that previously recorded in many prospective and retrospective trials, also to the best of our knowledge, this is the first study in Egypt and the Middle East comparing the three regimens simultaneously in adults as well as in juvenile proliferative LN.

Conclusion

During induction treatment of proliferative LN, high-dose CYC shows a better and rapid complete response after the sixth month of treatment in adults and juvenile LN patients, but after the first year of therapy, the three regimens have comparable efficacy and safety.

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Conflicts of interest

There are no conflicts of interest.

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