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ORIGINAL ARTICLE

Long-Term Renal and Fertility Outcomes after Lupus Nephritis Induction Therapy

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ABSTRACT

Background: Lupus nephritis (LN) may progress to loss of kidney function. Cyclophosphamide (CYC) and Mycophenolate Mofetil (MMF) are commonly used for induction therapy in LN. This study aimed to compare the long-term renal and fertility outcomes of CYC and MMF induction therapy in LN Egyptian patients.

Methods: A retrospective comparative study included 184 patients with LN class III and IV; 132 received CYC induction, and 52 received MMF. All their data were revised including history, examination, results of 1st renal biopsy, immunological markers, response to induction, relapse, maintenance therapy, and effects on renal functions and fertility.

Results: After 6 months of induction, remission was significantly higher in the MMF group (71.15%), than in the CYC group (37.12%) ($p<0.05$). There was a significant reduction in 24-hour urine proteins mean±SD (gm/day) in the CYC group from (4.5±2.2) to (2.6±0.6) ($p<0.05$), and in the MMF group from (5.4±2.8) to (3.3±0.8) ($p<0.05$). For maintenance, (61.36%) of the CYC induction group used steroid + Azathioprine (AZA), while (80.77%) of the MMF group used steroid + MMF ($p>0.05$). After long-term follow-up, complications occurred more in the CYC group (55%), compared to (34.6%) in the MMF group, with a statistically significant difference ($p<0.05$). But there was no statistically significant difference between the 2 groups as regards the renal outcome, or fertility ($p>0.05$).

Conclusions: MMF has a better remission rate in LN induction than CYC, but after long-term follow-up for maintenance therapy with steroid plus (AZA versus MMF), the renal and fertility outcomes were comparable in both groups.

Keywords: Lupus nephritis (LN); Cyclophosphamide (CYC); Mycophenolate Mofetil (MMF); Induction therapy; Fertility/Renal outcome.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disease [1], and diagnosis is made on history, examination, and autoantibodies like anti-neutrophil antibodies (ANA), and anti-double-stranded DNA (anti-ds-DNA) may be positive [2].

Nearly 50% of SLE patients develop lupus nephritis (LN), aggressive management is required to preserve kidney function [3], and renal biopsy is the gold standard for its diagnosis [4].

LN induction regimens include Cyclophosphamide (CYC) monthly for 6 months; Cyclophosphamide fortnightly for 3 months, or Mycophenolate Mofetil (MMF) for 6 months [5].

Jiang et al. reported that for LN induction, MMF is superior to CYC in improving serum complement C3 and complete remission, with fewer adverse drug reactions, while CYC is superior to MMF among Asian patients and in those with low baseline urine protein levels [6].

The adverse effects of CYC include leucopenia, infection, hemorrhagic cystitis, gonadal toxicity, infertility, and teratogenicity [7], but Luo et al. reported that the main adverse effects of CYC and MMF were infection and gastroenteritis [8].

Khattab et al. reported that CYC had much less cost in comparison to MMF, with no difference in efficacy, safety profile, or quality of life [9]. Repeated renal biopsies for LN patients should be a standard procedure to evaluate the response after immunosuppressive treatment [10].

There is still a debate as regards the efficacy and safety of CYC and MMF use for LN induction therapy, and their variability in different ethnic populations. Several studies showed similar efficacy, and low complete remission rates (30%), compared to biologic therapy [11]. Also, the long-term maintenance of immunosuppression and its risks and benefits especially on renal and fertility outcomes remains an area of controversy [12].

This study aimed to compare the long-term renal and fertility outcomes of CYC and MMF induction therapy in LN Egyptian patients.

METHODS

Study Design:

A retrospective comparative study was conducted on 184 female systemic lupus erythematosus (SLE) patients with biopsy-proven proliferative lupus nephritis (LN) class III and IV, who were under follow-up from January 2002 to December 2020 at the Urology and Nephrology Center, Mansoura University, Egypt. According to renal biopsy results, activity index (AI), and chronicity index (CI) [13], patients were divided into; Cyclophosphamide (CYC)-induction group; (132 patients), who were given intravenous (IV) cyclophosphamide 500 mg every 2 weeks for 6 doses (3 months), and Mycophenolate Mofetil (MMF)-induction group; (52 patients), who were given oral MMF 2 to 3 gm /day for 24 weeks.

Inclusion Criteria*:*

Female patients with SLE, age 18 to 55 years, with biopsy-proven LN class III and IV.

Exclusion Criteria:

Male patients, age less than 18 years, LN class I. II, V, and VI, patients who lost follow-up, and patients without available renal biopsy.

Ethical Approvals:

The protocol of this study had been approved by the Institutional Research Board (IRB) and Ethical Committee at the Faculty of Medicine, Zagazig University, Egypt, (ZU-IRB#:6860/18-4-2021), in addition to approvals from Mansoura Urology and Nephrology Center, Egypt. Consent had been taken from all participants, according to the Declaration of Helsinki.

Procedures:

All data were revised including past medical history, family history, clinical examination, and laboratory investigations including (urine analysis, 24-hour urinary protein, complete blood count (CBC), serum creatinine, albumin, total cholesterol, immunological [complement C3 and C4 levels, and anti-double stranded DNA (anti-ds-DNA)], histopathological details of renal biopsy class, activity, and chronicity indices and radiological assessment.

Data were collected at baseline (at the time of 1st renal biopsy) before induction therapy, and subsequently at 24 weeks (6 months) after induction therapy. Complete response (CR) was defined as a decrease in proteinuria to less than 0.5 gram/24 hours at the end of induction therapy. Partial response (PR) was defined as a decrease in proteinuria less than 50% of the baseline value at 24 weeks. Treatment failure was defined as urinary protein excretion that remains at/or >3.0 g/24 hour or an increase in proteinuria at the end of 24 weeks of therapy.

Complications were recorded (relapse, fertility problems, renal failure, infection, malignancy, drug toxicity, and shifting to other drugs). Data at the last follow-up <5 years, 5-10 years, or >10 years were also collected.

Statistical Analysis:

Data were analyzed using SPSS version 23.0. For baseline characteristics, we used mean±standard deviation (SD), and to compare the baseline characteristics and renal responses between the two treatment groups unpaired t-test and Chi-Square test were used. For comparison before and after treatment, we used paired t-test and Chi-Square test. Pearson's correlation

coefficient was used for the association between any two variables. The level of P <0.05 was considered the cut-off value for significance.

RESULTS

There was a statistically significant difference between the 2 groups at the time of the 1st renal biopsy and diagnosis of LN, as regards age in years, body mass index (BMI), complement C3 consumption, class of LN in renal biopsy, chronicity index, and the medications used for maintenance ($p<0.05$), with no significant difference as regards other parameters ($p>0.05$) (Table 1).

Age mean±SD was significantly higher in the CYC group (38.96±7.78) than in the MMF group (33.7±7.87) ($p<0.05$), and body mass index (BMI) was significantly higher in the CYC group (30.11±6.8) than in the MMF group (27.4±5.1) ($p<0.05$). Complement C3 consumption was more frequent in the CYC group (95.45%) than in the MMF group (88.4%) ($p<0.05$) (Table 1).

Most cases in the CYC group were class IV (59,1%), with (40.9%) class III, while most cases in the MMF group were class IV (75%), with (25%) class III ($p<0.05$). Most cases had a chronicity index (1-6), in (82.5%) of the CYC group, versus (76.9%) of the MMF group ($p<0.05$). For maintenance therapy after induction, most of the CYC group (78.8%) used azathioprine (AZA), while (94.2%) of the MMF group used MMF ($p<0.05$) (Table 1).

After 24 weeks (6 months) of induction, there was a statistically significant difference between the 2 groups as regards the frequency of remission, and the need for reinduction ($p<0.05$), with no significant difference as regards other parameters ($p>0.05$) (Table 2).

Total remissions were significantly higher in the MMF group (71.15%) than in the CYC group (37.12%) ($p<0.05$). Partial remission was significantly higher in the MMF group (38.46%) than in the CYC group (11.36%) ($p<0.05$). While treatment failure was significantly higher in the CYC group (62.87%) than in the MMF group (28.84%) ($p<0.05$). In the CYC group, the percentage who required re-biopsy (50%) was significantly higher than MMF group (21.2%) ($p<0.05$), and the percentage who required reinduction in the CYC group (35.6%) was significantly higher than in the MMF group (19.23%) ($p<0.05$) (Table 2).

After the completion of induction therapy in the CYC group, there was a statistically significant reduction in the mean±SD of the 24-hour urinary protein from (gm/day) (4.5±2.2) to (2.6±0.6) ($p<0.05$) and a statistically significant improvement of the immunological markers ($p<0.05$), but no significant effect on serum creatinine ($p>0.05$) (Table 3).

After the completion of induction therapy in the MMF group, there was a statistically significant reduction in the mean±SD of the 24-hour urinary protein (gm/day) from (5.4±2.8) to (3.3±0.8) ($p<0.05$) and a statistically significant improvement of the immunological markers ($p<0.05$), but no significant effect on serum creatinine ($p>0.05$) (Table 4).

After long-term follow-up (at least 5 years), there was a statistically significant difference between the 2 groups as regards maintenance therapy, frequency of complications, gastroenteritis, duration between completion of induction and the occurrence of malignancy, and percentage of patients seeking pregnancy ($p<0.05$), with no significant difference as regards other parameters ($p>0.05$). In most patients (58.69%), the duration of follow-up was 5-10 years, followed by (31.5%) <5 years, and (9.73%) >10 years. Most of the CYC induction group (61.36%) used steroid + Azathioprine (AZA) for maintenance, while most of the MMF group (80.77%) used steroid + MMF ($p<0.05$) (Table 5).

Complications occurred more frequently in the CYC group (55%), compared to (34.6%) in the MMF group, with a statistically significant difference ($p<0.05$). Gastroenteritis occurred more in the MMF group (15.3%) than in the CYC group (3.1%), with a statistically significant difference ($p<0.05$). Also, more females sought pregnancy in the CYC group (26.5%) than in the MMF group (5.7%), with a statistically significant difference ($p<0.05$). The mean±SD of the duration between induction completion and malignancy (in months) was

longer in the CYC group (20.6±3.2) than in the MMF group (18.3±1) (p<0.05) (Table 5 & Figure 1).

After long-term follow-up, there were no statistically significant differences between the CYC and the MMF induction groups, as regards the renal outcome (normal or impaired renal functions, proteinuria, progression to end-stage renal disease (ESRD), or the need for transplantation), fertility outcome (getting pregnant, infertility, the duration between completion of induction and getting pregnant, abortions, live births, or amenorrhea), avascular necrosis of femur, bacterial or CMV infection, pneumonia, urinary tract infection, cellulitis, treatment suspension, or malignancy (p>0.05) (Table 5 & Figure 1).

Table (1): Baseline demographic and clinical characteristics of LN patients at the time of the 1st renal biopsy receiving CYC and MMF induction.

Variable	Cyclophosphamide (CYC) induction (n=132)	Mycophenolate Mofetil (MMF) induction (n=52)	Test of Signif	P-value
Age (years) mean±SD	38.96±7.78	33.7±7.87	t=4.12	**<0.05***
BMI (Kg/m2) mean±SD	30.11±6.8	27.4±5.1	t=2.4	**<0.05***
S. creatinine ≥1.4 mg/dL	36 (27.5%)	16 (30.8%)	X2=0.198	0.65
Proteinuria:			X2=0.524	0.469
Non-nephrotic range	47 (36.4%)	16 (30.8%)		
Nephrotic range	82 (63.6%)	36 (69.2%)		
S. albumin (g/dL) mean±SD	2.68±0.7	2.7±0.8	t=0.924	0.37
S. cholesterol (mg/dL) mean±SD	244.88±72.4	237.55±69.48	t=0.622	0.53
Hemoglobin (g/dL) mean±SD	9.6±1.9	9.8±2.3	t=0.787	0.469
White blood cells (10^3/mm^3) mean±SD	7.5±3.3	7.5±4	t=0.08	0.941
Platelets (10^3/mm^3) mean±SD	261.1±103.2	261.03±105.2	t=0.004	0.997
Positive Anti-ds-DNA	121 (91.67%)	46 (88.4%)	X2=0.457	0.2
Consumed C3	126 (95.45%)	46 (88.4%)	X2=3.9	**<0.05***
Consumed C4	113 (85.6%)	42 (81.76%)	X2=0.65	0.0.66
LN class III	54 (40.9%)	13 (25%)	X2=4.078	**<0.05***
LN class IV	78 (59.1%)	39 (75%)		
Activity index:			X2=2.45	0.4
≥10	71 (53.8%)	25 (48.1%)		
<10	61 (46.2%)	27 (51.9%)		
Chronicity index:			X2=15.46	**<0.05***
>6	2 (1.6%)	1 (1.9%)		
1-6	109 (82.5%)	40 (76.9%)		
0	15 (11.9%)	11 (21.2%)		
Pulse steroid in induction	43 (32.6%)	16 (30.8%)	X2=0.056	0.813
Chloroquine in induction	112 (84.8%)	46 (88.5%)	X2=5.35	0.316
Maintenance treatment:				**<0.05***
Azathioprine	104 (78.8%)	3 (5.8%)	X2=94.74	
MMF	24 (18.2%)	49 (94.2%)		

Variable	Cyclophosphamide (CYC) induction (n=132)	Mycophenolate Mofetil (MMF) induction (n=52)	Test of Signif	P-value
Cyclosporine	4 (3%)	0		
Additional treatment:				
Plasma exchange	7 (5.3%)	3 (5.8%)	X2=0.016	0.9
IVIG	1 (0.8%)	2 (3.8%)	X2=2.219	0.136

*P<0.05 statistically significant. t (t-test). X2 (Chi-Square). BMI (body mass index). S. (serum). Anti-ds-DNA (anti-double-stranded DNA). C3 (complement 3). C4 (complement 4). LN (lupus nephritis). IVIG (intravenous immunoglobulin).

Table (2): Renal outcomes after 6 months of 1st induction therapy.

Variable	Cyclophosphamide (CYC) induction (n=132)	Mycophenolate Mofetil (MMF) induction (n=52)	Test of Signif x2	P-value
Serum creatinine ≥1.4 mg/dL	40 (31.5%)	15 (29.4%)	0.074	0.786
No proteinuria **Non-nephrotic range** **Nephrotic range**	34 (25.7%) 65 (49.2%) 33 (25.1%)	17 (32.7%) 18 (34.6%) 17 (32.7%)	2.44	0.118
Positive anti-ds-DNA	11 (11.3%)	4 (12.1%)	4.3	0.634
Consumed C3	12 (12.9%)	4 (12.1%)	2.84	0.241
Consumed C4	8 (8.6%)	2 (6.1%)	3.017	0.22
Total remissions	49 (37.12%)	37 (71.15%)	18.69	**<0.05***
Complete remission	34 (25.37%)	17 (32.69%)	0.998	0.3177
Partial remission	15 (11.36%)	20 (38.46%)	17.692	**<0.05***
Treatment failure	83 (62.87%)	15 (28.84%)	17.259	**<0.05***
No response	17 (12.87%)	4 (7.69%)	0.99	0.3
Need for re-biopsy (Worsening)	66 (50%)	11 (21.2%)	12.76	**<0.05***
Need for reinduction	47 (35.6%)	10 (19.23%)	4.68	**<0.05***

*P<0.05 statistically significant. X2 (Chi-Square). Anti-ds-DNA (anti-double-stranded DNA). C3 (complement 3). C4 (complement 4).

Table (3): Comparison of renal functions and immunological markers in LN patients before and after the completion of 1st induction therapy in the CYC group.

Cyclophosphamide induction	Before treatment	After treatment	Test of Signif	P-value
Renal impairment (serum creatinine) (S. Cr) ≥1.4 mg/dL)	36 (27.5%)	40 (31.5%)	X2=0.29	0.58
Serum creatinine (mg/dL) mean±SD	1.4±0.7	1.5±0.7	t=1.16	0.24
No proteinuria **Non-nephrotic**	0 47 (36.4%)	34 (25.7%) 65 (49.2%)	X2=54.87	**<0.05***

Cyclophosphamide induction	Before treatment	After treatment	Test of Signif	P-value
Nephrotic range	82 (63.6%)	33 (25.1%)		
Proteinuria (g/24 h) mean±SD	4.5±2.2	2.6±0.6	t=9.57	**<0.05***
Positive anti-ds-DNA	121 (91.67%)	11 (11.3%)	X2=183.33	**<0.05***
Consumed C3	126 (95.45%)	12 (12.9%)	X2=184.1	**<0.05***
Consumed C4	113 (85.6%)	8 (8.6%)	X2=192.3	**<0.05***

*P<0.05 statistically significant. t (t-test). X2 (Chi-Square). Anti-ds-DNA (anti-double-stranded DNA). C3 (complement 3). C4 (complement 4).

Table (4): Comparison of renal functions and immunological markers in LN patients before and after the completion of 1st induction therapy in the MMF group.

Mycophenolate Mofetil induction	Before treatment	After treatment	Test of Signif	P-value
Renal impairment (serum creatinine) (S. Cr) ≥1.4 mg/dL)	16 (30.8%)	15 (29.4%)	X2=0.037	0.56
Serum creatinine (mg/dL) mean±SD	1.4±0.4	1.3±0.5	t=1.126	0.26
No proteinuria **Non-nephrotic** **Nephrotic range**	0 16 (30.8%) 36 (69.2%)	17 (32.7%) 18 (34.6%) 17 (32.7%)	X2=21.14	**<0.05***
Proteinuria (g/24 h) mean±SD	5.4±2.8	3.3±0.8	t=5.2	**<0.05***
Positive anti-ds-DNA	46 (88.4%)	4 (12.1%)	X2=43.52	**<0.05***
Consumed C3	46 (88.4%)	4 (12.1%)	X2=43.52	**<0.05***
Consumed C4	42 (81.76%)	2 (6.1%)	X2=36.9	**<0.05***

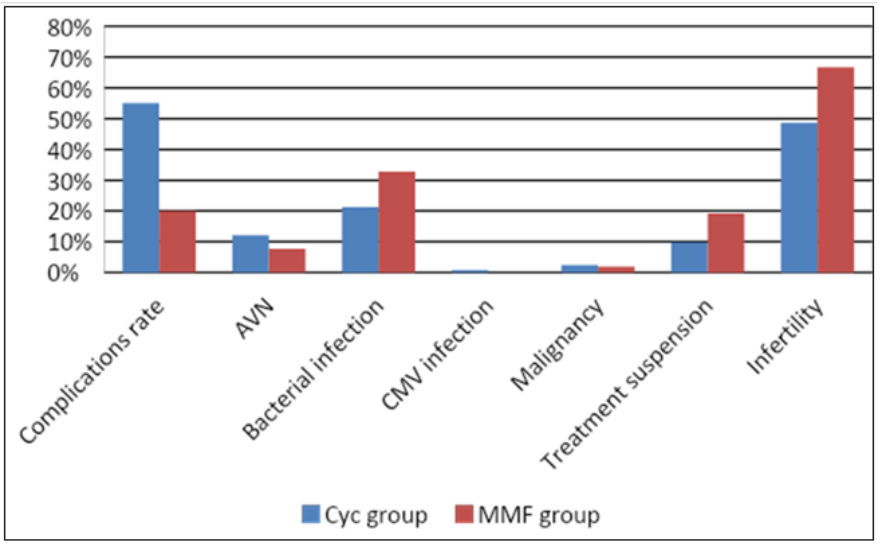
*P<0.05 statistically significant. t (t-test). X2 (Chi-Square). Anti-ds-DNA (anti-double-stranded DNA). C3 (complement 3). C4 (complement 4).

Table (5): Long-term follow-up of renal and fertility outcomes and adverse effects of lupus nephritis therapy (at least 5 years).

Variable	Cyclophosphamide (CYC) induction (n=132)	Mycophenolate Mofetil (MMF) induction (n=52)	Test of Signif	P-value
Duration of follow-up: **<5 years** **5-10 years** **>10 years**	 58 (31.5%) 108 (58.69%) 18 (9.73%)			
Normal renal function	89 (67.4%)	38 (73.1%)	X2=0.557	0.455
Impaired renal function	35 (26.5%)	11 (21.15%)	X2=0.57	0.449
End-stage renal disease	8 (6.06%)	3 (5.7%)	X2=0.056	0.94
Proteinuria: **Non-nephrotic range** **Nephrotic range**	 111 (84.09%) 21 (15.91%)	 41 (78.8%) 11 (21.2%)	X2=0.71	0.398
Kidney transplant	1 (0.8%)	0	X2=0.402	0.526
Maintenance immunosuppression: **None**	 15 (11.36%) 81 (61.36%)	 5 (9.6%) 3 (5.77%)		

Variable	Cyclophosphamide (CYC) induction (n=132)	Mycophenolate Mofetil (MMF) induction (n=52)	Test of Signif	P-value
Steroid+Azathioprine **Steroid+MMF**	36 (27.27%)	42 (80.77%)	X2=51.37	**<0.05***
Cumulative dose: **6 doses (3 gm)** **12 doses (6 gm)** **18 doses (9 gm)**	 122 (92.4%) 7 (5.3%) 3 (2.27%)			
Frequency of complications	72 (55%)	18 (34.6%)	X2=5.9	**<0.05***
Avascular hip necrosis	16 (12.1%)	4 (7.7%)	X2=0.755	0.385
Bacterial infection	28 (21.2%)	17 (32.7%)	X2=2.66	0.1
CMV infection	1 (0.8%)	0	X2=0.98	0.2
Time of infection: **During induction** **After completion of induction**	 19 (14.4%) 10 (7.5%)	 14 (26.9%) 3 (5.7%)	 X2=1.5	 0.22
Type of infection: **Pneumonia** **Urinary tract infection** **Cellulitis** **Gastroenteritis**	 11 (8.3%) 11 (8.3%) 2 (1.5%) 4 (3.1%)	 4 (7.6%) 5 (9.6%) 0 (0%) 8 (15.3%)	 X2=0.02 X2=0.077 X2=0.021 X2=9.34	 0.88 0.78 0.88 **<0.05***
Treatment suspension	13 (9.84%)	10 (19.23%)	X2=3.002	0.083
Malignancy	3 (2.4%)	1 (1.9%)	X2=0.96	0.8
Type of malignancy: **Kaposi Sarcoma** **Non-Hodgkin lymphoma** **Breast cancer**	 1 (0.76%) 1 (0.76%) 1 (0.76%)	 0 1 (1.9%) 0	 X2=0.98	 0.3
Timing for malignancy: **During induction** **After completion of induction**	 0 3 (2.4%)	 0 1 (1.9%)	 X2=0.38	 0.5
The duration between induction completion and malignancy (months) mean±SD	20.6±3.2	18.3±1	t=5.173	**<0.05***
Effect on fertility **Sought pregnancy**	35 (26.5%)	3 (5.7%)	X2=9.7	**<0.05***
Incidence of pregnancy: **Got pregnant** **Infertile**	 18/35 (51.4%) 17/35 (48.6%)	 1/3 (33.33%) 2/3 (66.67%)	 X2=0.36	 0.54
Pregnancy outcome: **Abortion** **Live birth**	 5/35 (14.29%) 13/35 (37.14%)	 0 1/3 (33.33%)	 X2=0.11	 0.74
The duration between induction completion and pregnancy (months) mean±SD	14.32±2.1	13.95±2.3	t=1.047	0.29
Amenorrhea	14 (10.6%)	9 (17.3%)	X2=1.66	0.19

*P<0.05 statistically significant. t (t-test). X2 (Chi-Square). CMV (cytomegalovirus).



AVN (avascular hip necrosis). CMV (cytomegalovirus). CYC (cyclophosphamide-induction group). MMF (mycophenolate mofetil-induction group).

Figure (1): Frequency of long-term complications in the 2 induction groups.

DISCUSSION

Lupus nephritis (LN) usually occurs 3-5 years after the diagnosis of systemic lupus erythematosus (SLE), and histopathological evidence is detected in most patients, even without clinical evidence. Early diagnosis and proper treatment are mandatory to improve renal outcomes in LN patients [14].

This is a retrospective comparative, long-term follow-up study on systemic lupus erythematosus (SLE) Egyptian female patients with biopsy-proven lupus nephritis (LN) class III and IV. Data obtained from Mansoura Urology and Nephrology Center, Egypt, included 184 patients: 132 LN patients who received cyclophosphamide (CYC) induction, and 52 patients who received MMF induction.

The mean age for the CYC group was higher than for the MMF group. This may be explained by the fact that young patients are more concerned about the adverse effects of the CYC on fertility [15].

Most of the studied LN patients had class IV LN (63.5%), while class III was present in 36.5% of patients. Most patients were class IV in the CYC induction group (59.1%), versus (75%) in the MMF induction group. This was comparable with Khattab et al., who made a retrospective study that included 122 patients with LN class III, IV, and V, 61 patients received CYC, while 61 patients received MMF. 54% of his class III LN patients received CYC, compared to 39% of class III who received MMF, while 49% of class IV patients received MMF and 27% with class IV LN received CYC [9].

Most of the CYC induction group continued maintenance therapy with steroid and azathioprine (AZA) (78.8%), compared to (5.8%) in the MMF group, while most of the MMF group continued maintenance therapy on steroids and MMF (94%). This point is so important, because of the cost/benefit differences. The first combination is much less in cost than the MMF. The high cost of the MMF may cause non-compliance and treatment failure in low socioeconomic cases. Oral CYC daily is well tolerated but has the risk of causing hemorrhagic cystitis, which is rare in IV CYC [16].

After 6 months of induction, total remissions were higher in the MMF group (71.15%) compared to the CYC group (37.12%). This may be due to higher chronicity in the CYC

group before receiving induction [17] but may be related to the difference in the number of patients in each group. The activity index (AI) reflects the degree of inflammatory injury to the renal parenchyma that may be a response to immunosuppressive therapy, while the chronicity index (CI) reflects the degree of chronic damage to the kidney that may be refractory to aggressive therapy [18].

Jiang et al. found that MMF was better than CYC in increasing serum complement C3 and complete remission of LN. In Asian, but not Caucasian patients, CYC had a better effect on decreasing proteinuria than MMF, especially in patients with initial proteinuria less than 4 gm/day, but no difference in improving serum creatinine [19]. This contrasts with Rathi et al., who found no significant differences between CYC and MMF groups [20].

Half of the CYC group (50%) required re-biopsy for worsening of their condition and (35.6%) re-induction due to worsening of renal function or persistent proteinuria, while in the MMF group, the percentage was significantly lower (21.1%) and (19.23%). Sedhain et al. found that a low dose of MMF was as effective as IV CYC in inducing remission, reduction of proteinuria, and improvement of renal function with more safety in proliferative LN after 6 months therapy in the Nepalese population [21].

In both groups, proteinuria, positive anti-ds-DNA, and consumed C3 significantly improved after induction, with no significant improvement in serum creatinine. This agrees with the findings by Choi et al., who also found that proteinuria decreased significantly after CYC or MMF induction in LN [22].

At the last follow-up visit (at least 5 years) after long-term maintenance therapy, most of the CYC induction group (61.3%) were maintained on steroid + azathioprine (AZA), while most of the MMF group (80.7%) were maintained on steroid + MMF, with no difference in the renal outcome; relapse rate, proteinuria, effect on renal function, or progression to end-stage renal disease (ESRD) in both groups. This agrees with Ahmad et al., who recommended maintenance therapy with MMF or AZA, rather than CYC for LN [23].

Regarding long-term complications, in our study (54%) of the CYC induction group had a significantly higher frequency of complications compared to (34.6%) of the MMF group. Both groups were comparable regarding the incidence of avascular hip necrosis, bacterial or CMV infection, pneumonia, urinary tract infection, and cellulitis, while gastroenteritis was significantly higher among MMF. Most infections occurred during the induction therapy, which lead to the suspension of treatment in (9.8%) of the CYC group, and (19.2%) in the MMF group.

Feldman et al. found no difference between CYC and MMF induction groups as regards infectious complications [24], while Joe et al. reported that the most common adverse effects were infection and hematological abnormalities such as neutropenia and aplastic anemia, with no difference between CYC and MMF groups [25]. Mendonca et al. found that vomiting was more frequent with CYC, while diarrhea was more frequent with MMF [26].

Malignancy occurred in our study patients 1.5 to 2 years after completion of induction therapy, and the incidence of malignancy was higher among the CYC group (2.4%) compared to the MMF group (1.9%), with no significant difference. Three patients had malignancy in the CYC group; one Kaposi sarcoma, one non-Hodgkin lymphoma, and one breast cancer compared to one patient who had non-Hodgkin lymphoma in the MMF group. The carcinogenic effect of CYC may be related to its cumulative dose, and if the cumulative dose of oral CYC does not exceed 10 gm, then malignancy rarely occurs. Calatroni et al. reported that CYC can increase the risk of skin cancer, non-Hodgkin lymphoma, and bladder cancer [27].

As regards fertility, most of our patients were maintained on birth control due to the instability of renal function and proteinuria. Among the CYC group, (26.5%) of patients sought pregnancy, versus (5.7%) in the MMF group. The mean duration between completion of induction and the occurrence of pregnancy,

was around 14 months in both groups. Pregnancy was higher in the CYC group (51.4%), versus (33.3%) in the MMF group, but with no statistical significance. Sharma et al. reported that ovarian dysfunction in LN patients with monthly intravenous CYC was subclinical, negatively affecting ovarian reserve, but no premature ovarian failure at 1 year. While they found no ovarian dysfunction in the MMF group [28].

Alarfaj et al. studied the effects of CYC on fertility in Saudi women and found that (48.5%) of the CYC induction group got pregnant, versus (58.2%) in the non-CYC group, with a similar rate of abortion, still-birth, and live-birth. Also, amenorrhea was higher in the CYC group (28.2%), versus (3.7%) in the non-CYC group [29].

Genetic factors of different ethnicities are associated with the risk of LN in SLE patients. This explains the clinical heterogeneity of LN risk and response to therapy between different ethnic groups [30]. Black and Hispanic patients achieve remission more likely with MMF, while in patients presenting with more severe renal disease, CYC may be preferred [31].

Although in our study, the age in the CYC group was higher than in the MMF group, the studied females were still within child-bearing age at the time of induction therapy. The cumulative dose in most patients did not exceed 3 grams and its dose was not dependent on the body weight. Kim et al. mentioned that the cumulative exposure to CYC should be reduced, as 15–20 grams may cause infertility in >50% of females >30 years, and the risk is lower in younger patients [7].

The difference in LN class in renal biopsy and the chronicity index between the 2 groups might have affected the response to induction therapy. The higher chronicity index in the CYC group may explain the better remission achieved by the MMF, which has a lower chronicity index. Park et al. showed that complete remission in LN patients was dependent on the duration, chronicity index, erythrocyte sedimentation rate, glomerular sclerosis, interstitial fibrosis, tubular atrophy, and the use of hydroxychloroquine. Also, the presence of glomerular sclerosis in the chronicity index was an independent predictor of complete remission after induction therapy in these patients [32].

Points of Strength: This study included Egyptian patients with LN, with detailed data, showing the sequence of responses, and relapses, and focusing on long-term renal and fertility outcomes.

Limitations of the study: This study was a single-center study, and the included number of patients was relatively small. The number of patients using the CYC for induction was more than those using the MMF, because of the low cost of the CYC, making it more widely used in LN induction.

Recommendations: Further studies comparing groups with equal numbers of patients are recommended for better comparison between CYC and MMF use for induction therapy in LN Egyptian patients. Also, the results of repeated renal biopsies should be compared for a better comparison.

CONCLUSIONS

MMF has a better remission rate in LN induction than CYC, but after long-term follow-up for maintenance therapy with steroid plus (AZA versus MMF), the renal and fertility outcomes were comparable in both groups.

Conflicts of Interest/Financial Disclosures: None.

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