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Re-Biopsy for Proliferative Lupus Nephritis in Egyptian Female Patients: A Single-Center Study

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ABSTRACT

Background: Renal biopsy is the golden tool for the diagnosis of proliferative lupus nephritis (LN), the level of histological activity, and the risk of end-stage renal disease (ESRD).

Objective: This study aimed to investigate the value of repeated renal biopsy in the follow-up of proliferative LN patients and to determine the predictors for re-biopsy and re-induction.

Methods: A retrospective study made on 184 LN Egyptian females, data from 2002 to 2020 included history, examination, laboratory investigations, and results of repeated biopsies.

Results: Remission was achieved in 46.7% of patients versus 53.3% with non-remission. The non-remission was significantly higher with higher chronicity index (CI), CYC 1ry induction, and AZA 1ry maintenance than with lower CI, MMF 1ry induction, or maintenance (S). About 41.8% of patients had a 2nd biopsy, and 30.9% received re-induction therapy. Significant predictors for non-responding included type of 1ry induction and activity index (AI). In the CYC 1ry induction group, the AI mean±SD in 2nd biopsy (6.83 ±4.02) was significantly lower than in 1st biopsy (10.6 ±4.08) (S), while the CI mean±SD in 2nd biopsy (3.4 ±1.4) was significantly higher than in 1st biopsy (2.5 ±1.2) (S), with no significant difference in the MMF group. Out of the 184 LN patients who had their 1st biopsy, 77 patients (41.8%) had a 2nd biopsy, with no difference as regards the class of LN, but the AI mean±SD was significantly lower in the 2nd biopsy (7.4±4.2) compared to 1st biopsy (10.0±4.4) (S), while the CI mean±SD was higher in the 2nd biopsy (3.0±2.3) compared to the 1st biopsy (2.4±1.6) (S).

Conclusions: Repeated renal biopsies are important in the follow-up of Egyptian female patients with proliferative LN, after 1ry induction therapy or an event-based biopsy. The use of MMF reduces the risk for non-remission, and the need for re-biopsy, or re-induction.

Keywords: Lupus nephritis (LN), Re-induction; Re-biopsy, Cyclophosphamide (CYC), Mycophenolate Mofetil (MMF).

INTRODUCTION

The development of lupus nephritis (LN) in patients with systemic lupus erythematosus (SLE) occurs due to several factors including apoptosis, autoantibodies, complement activation, and immune complex formation [1].

For the diagnosis of LN and guidance for therapy, renal biopsies play a crucial role [2]. The risk of end-stage renal disease (ESRD) is high in patients with biopsy-proven class III and IV (proliferative) lupus nephritis (LN) [3].

Although most patients with proliferative LN remain proliferative in repeated renal biopsy, it is still recommended to identify the ones that switch to a non-proliferative class as they make up 20% of cases. Repeated biopsy can also assist in identifying cases with proliferative LN with progression and the need to intensify, reduce, or replace immunosuppression [4].

Short and intensive induction therapy with immunosuppression is typically the approach for managing proliferative LN (3-6 months) followed by maintenance therapy [5]. Corticosteroids, intravenous and oral cyclophosphamide, as well as mycophenolate mofetil (MMF), are commonly used for this purpose[6], but new strategies include multitarget therapy with calcineurin inhibitors and B-cell depletion therapy [7].

Response to current therapy may be delayed and less than 50% of LN patients achieve complete remission and proteinuria <0.5 g/24 hours after 12 months [8], and complete remission was associated with chronicity index on renal biopsy, disease duration, and early hydroxychloroquine use [9]. Moreover, the severity of LN and the response to various types of therapy vary according to ethnicity and race [10].

This study aimed to investigate the value of repeated renal biopsy in the follow-up of proliferative LN patients and to determine the predictors for re-biopsy and re-induction.

PATIENTS AND METHODS

Study Design:

This retrospective cohort study had been carried out on a total of 184 Egyptian females diagnosed with lupus nephritis (LN), class III and class IV (proliferative), with their mean age±SD (36.33±7.82) years. Data were reviewed for patients attending Urology and Nephrology Center, at Mansoura

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University, Egypt, from January 2002 to December 2020. After completion of the first induction therapy, 77 patients (41.8%) required re-biopsy, and 57 patients (30.9%) required re-induction.

Inclusion Criteria:

Female patients diagnosed with biopsy-proven LN class III and IV, age above 18 years and less than 55 years.

Exclusion Criteria:

Male patients, female patients less than 18 years or above 55 years, other LN classes in the biopsy, patients without available renal biopsy, or those who lost their follow-up.

Procedures:

Required data were reviewed and collected including history, examination, laboratory, and radiological data. Laboratory tests included complete blood picture (CBC), serum creatinine, serum albumin, serum total cholesterol, complement C3 and C4, anti-double-stranded DNA (anti-ds-DNA) and 24-hour urinary protein. The results of the 1st, 2nd, and 3rd renal biopsies were obtained (when available), including the class of LN, activity index (AI) (0-24) and chronicity index (CI) (0-12) [11].

After the completion of 6 months' induction therapy, the clinical outcome was defined as complete remission (CR) (return of serum creatinine to the previous baseline value, and/or reduction of 24-hour urinary protein to less than 0.5 gm/24 hours), partial remission (PR) (partial improvement in serum creatinine but not to normal, and/or reduction of 24-hour urinary protein to less than 50% of previous baseline), no remission, or deterioration [12].

Ethical Approvals:

Ethical approval No. ZU-IRB#:6860/18-4-2021, was obtained from the Ethical Committee and the Institutional Research Board (IRB), Faculty of Medicine, Zagazig University, Egypt. Approvals were obtained also from the Urology and Nephrology Center, Mansoura University, Egypt. Consent was obtained from all participants, according to Helsinki's Declaration.

Statistical Analysis

Data were analyzed using SPSS version 23.0. The mean± SD (standard deviation) was used for baseline data. Paired t-test, unpaired t-test, and Chi-Square test were used for comparison, as required. Univariate and multivariate analysis and adjusted prediction models were used when appropriate. The P-value <0.05 was considered significant.

RESULTS

This study involved 184 Egyptian female patients with biopsy-proven lupus nephritis (LN), who received 1ry induction therapy. Out of these, 46.7% achieved remission, while 53.3% did not. A comparison was made between the two groups based on certain parameters such as the activity index (AI), chronicity index (CI), and the type of induction and maintenance therapy. The only significant difference between the two groups was observed in CI, and the type of therapy (Table 1).

The remission group had a statistically significantly lower mean value of CI compared to the non-remission group. Furthermore, 56.9% in the remission group received CYC and 44.1% MMF for 1ry induction, while 84.7% in the non-remission group received CYC and 14.3% MMF (S). After 1ry induction, patients received maintenance therapy with AZA, MMF, or cyclosporine (Table 1).

Table (1): Comparison of the LN groups with and without remission after the 1ry induction therapy as regards demographic data, laboratory tests, 1st biopsy results, type of 1ry induction and 1ry maintenance, and complications of therapy

Variables	Remission (86 patients)	Non- remission (98 patients)	Test of significance	P-value
Age (years) mean±SD	36.4±7.5	38.9±8.7	t=-0.8	0.12
Age at the time of SLE diagnosis (years) mean±SD	25.1±12.1	24.7±9.4	t=-0.2	0.8
Age at the time of LN diagnosis (years) mean±SD	26.6±7.6	27.1±8.9	t=0.41	0.06
Hypertension	66 (76.6%)	81 (83.1%)	X^2=0.9	0.23
Diabetes mellitus	7 (8.4%)	9 (9.1%)	X^2=0.06	0.8
Hepatitis C	3 (3.8%)	4 (3.9%)	X^2=0.0.3	0.9
Antiphospholipid syndrome	16 (18.7%)	19 (19.5%)	X^2=0.02	0.9
Thrombotic events	11 (13.1%)	14 (14.3%)	X^2=0.08	0.82
Neurologic manifestations	8 (9.3%)	18 (18.2%)	X^2=3.1	0.08
Renal impairment (serum creatinine ≥1.4 mg/dL)	26 (30.2%)	25 (26%)	X^2=0.5	0.5
Non-nephrotic proteinuria **Nephrotic proteinuria**	30 (34.9%) 56 (65.1%)	34 (34.7%) 64 (65.3%)	X^2=0.0006	0.9
Serum creatinine (mg/dL) mean±SD	1.48±0.36	1.42±0.34	t=-0.84	0.9
Proteinuria (g/24 h) mean±SD	4.8±1.2	4.6±1.14	t=-1.00	0.48
Serum albumin (g/dL) mean±SD	2.8±0.7	2.5±0.6	t=-0.9	0.8
Serum cholesterol (g/dL) mean±SD	241.8±59.4	244.16±60.6	t=0.2	0.5
Hemoglobin (g/dL) mean±SD	9.7±2.1	9.5±1.8	t=-0.6	0.15
White blood cells (10^3/mm^3) mean±SD	7.7±1.8	7.2±1.7	t=-0.9	0.4
Platelets (10^3/mm^3) mean±SD	262.6±64.9	258.9±63.6	t=-0.24	0.6
Positive anti-Ds-DNA (IU/ml)	79 (92%)	95 (97.4%)	X^2=2.29	0.4
Reduced C3 (mg/dl)	79 (91.3%)	92 (94.3%)	X^2=2.47	0.5
Reduced C4 (mg/dl)	63 (91.3%)	93 (94.1%)	X^2=2.76	0.6
Lupus nephritis (LN) class: **Class III** **Class IV**	 31 (35.5%) 55 (64.5%)	 37 (37.7%) 61 (62.3%)	X^2=0.057	0.7
Activity index (AI): ≥10 **<10**	42 (49.5%) 44 (50.5%)	58 (59.7%) 40 (40.2%)	X^2=1.97	0.06
AI mean±SD	9.5±4.6	10.8±4.09	t=1.9	0.15
Chronicity index (CI): >6 **1-6** **0**	3 (2.8%) 67 (77.6%) 16 (19.6%)	4 (3.8%) 88 (89.6%) 6 (6.5%)	X^2=6.7	**0.04***
CI mean±SD	2.4±1.3	2.5±1.3	t=2.6	**0.002***
Pulse steroid	25 (29%)	36 (36.4%)	X^2=1.2	0.28
1ry induction: **Cyclophosphamide (CYC)** **MMF**	 49 (56.9%) 38 (44.1%)	 83 (84.7%) 14 (14.3%)	X^2=12.9	**0.0001***
Chloroquine use **Un-reported**	66 (76.4%) 20 (23.6%)	76 (77.9%) 22 (22.1%)	X^2=0.017	0.81
1ry maintenance: **Azathioprine (AZA)** **MMF** **Cyclosporine**	 42 (48.6%) 42 (48.6%) 2 (2.8%)	 67 (68.8%) 24 (24.7%) 7 (7.2%)	X^2=12.6	**0.003***
Complications	40 (46.2%)	52 (53.2%)	X^2=0.7	0.3
Bacterial infection	19 (22.4%)	27 (27.3%)	X^2=0.2	0.4
CMV (cytomegalovirus) infection	0	1 (1.02%)	X^2=0.22	0.4
Malignancy	3 (3.4%)	1 (1.02%)	X^2=0.36	0.49

X^2= Chi-square test. t= student t-test. *= Significant.

The results of the study showed that after the initial 6 months of induction therapy, the group of patients who received MMF had a statistically significantly higher rate of remission compared to those who received CYC. Out of the total 184 LN patients, 41.8% required a 2nd biopsy, and 30.9% needed re-induction. Within the CYC group, 50% of patients needed a 2nd biopsy, and 35.6% required re-induction, compared to 21.2% and 19.23% in the MMF group. The CYC group had a remission rate of 37.2%, with 25.1% achieving complete remission (CR) and 11.1% partial remission (PR), while the MMF group had a remission rate of 71.2%, with 32.7% achieving CR and 38.5% PR, and 28.8% non-remission (Table 2).

Table (2): Renal outcome in LN patients (6 months after 1ry induction completion)

Variables	CYC induction (132 patients)	MMF induction (52 patients)	Test of Significance	P-value
Renal impairment (Serum creatinine ≥1.4 mg/dL)	40 (31.5%)	15 (29.4%)	X^2= 0.07	0.7
No proteinuria Non-nephrotic Nephrotic range	34 (25.7%) 65 (49.2%) 33 (25.1%)	17 (32.7%) 18 (34.6%) 17 (32.7%)	X^2= 2.4	0.2
S. creatinine (mg/dL) mean±SD	1.5±0.36	1.3±0.31	t= 0.93	0.2
Urinary proteins (g/24 h) mean±SD	2.6±0.6	3.3±0.8	t= -1.5	0.1
Positive anti-Ds-DNA (IU/ml)	11 (11.3%)	4 (12.2%)	X^2= 4.3	0.6
Reduced C3 (mg/dl)	12 (12.9%)	4 (12.2%)	X^2= 2.84	0.2
Reduced C4 (mg/dl)	8 (8.6%)	2 (6.1%)	X^2= 3.01	0.2
Total remissions Complete remission (CR) Partial remission (PR)	49 (37.2%) 34 (25.1%) 15 (11.1%)	37 (71.2%) 17 (32.7%) 20 (38.5%)	X^2= 18.6 X^2=0.9 X^2=17.6	**0.03*** 0.33 **0.04***
Non-remission	83 (62.7%)	15 (28.8%)	17.2	**0.03***
Need for reinduction	47 (35.6%)	10 (19.2%)	X^2= 4.68	**0.04***
Need for re-biopsy (Worsening)	66 (50%)	11 (21.2%)	X^2= 12.7	**0.0001***

S= Serum. X^2= Chi-square test. t= student t-test. *= Significant.

The use of multivariate analysis, specifically linear regression, and binary logistic regression to identify the risk factors for non-response to 1ry induction therapy did not yield any significant results for any parameter (Table 3). However, when using an adjusted prediction model for binary logistic regression, the type of induction and activity index were found to be significant predictors for non-response to 1ry induction (Table 4).

Table (3): Multivariate analysis of risk factors for non-responding to the 1ry induction therapy

Variables	B estimates	95% confidence interval		P-value
		Lower	Upper	
Age	-0.314	-0.067	0.024	0.35
Age at the time of lupus diagnosis	0.039	-0.054	0.059	0.93
Age at the time of nephritis diagnosis	0.538	-0.034	0.102	0.314
Hypertension	0.203	-0.102	0.537	0.177
Diabetes mellitus	-0.245	-0.894	0.109	0.122
Hepatitis C	-0.064	--1.038	0.69	0.69
Antiphospholipid syndrome	0.036	0.36	0.84	0.39
Thrombotic events	0.068	-0.31	0.483	0.66
Neurologic manifestations	0.216	-0.21	0.85	0.23
S. creatinine (mg/dL)	-0.007	-0.124	0.119	0.97
Urinary proteins (g/24 hours)	0.079	-0.035	0.058	0.63
S. albumin (g/dl)	-0.021	-0.235	0.21	0.912
S. cholesterol (mg/dl)	0.045	-0.002	0.003	0.785
Positive anti-Ds-DNA (IU/ml)	0.227	-0.259	1.137	0.21
Consumed C3 (mg/dl)	0.07	-0.512	0.795	0.65
Consumed C4 (mg/dl)	0.081	-0.33	0.569	0.65
Lupus nephritis (LN) class	0.115	-0.321	0.444	0.526
Activity index (AI)	-0.191	0.06	0.022	0.36
Chronicity index (CI)	-0.124	-0.122	0.056	0.46
Pulse steroid	-0.071	-0.408	0.263	0.66
Type of induction	-0.067	-0.498	0.356	0.739
Type of maintenance	-0.045	-0.313	0.243	0.8

Regression analysis using linear regression analysis and binary logistic regression.

Table (4): An adjusted prediction model for predictors of non-responding including serum creatinine, proteinuria, induction, maintenance therapy, activity, and chronicity indices

1st adjusted model	B estimates	95% confidence interval		P-value
		Lower	Upper	
S. creatinine (mg/dl)	0.074	-0.026	0.076	0.337
Urinary proteins (g/24 hours)	-0.004	-0.023	0.022	0.958
Type of induction	0.231	0.066	0.431	**0.008***
Type of maintenance	0.084	-0.067	0.199	0.328
Activity index (AI)	-0.192	-0.038	-0.004	**0.015***
Chronicity index (CI)	-0.102	-0.073	0.014	0.182
2nd adjusted model	**B estimates**	**95% confidence interval**		**P value**
		Lower	**Upper**	
Type of induction	0.226	0.065	0.425	**0.008***
Type of maintenance	0.083	-0.066	0.199	0.327
Activity index (AI)	-0.167	-0.035	-0.002	**0.025***
Chronicity index (CI)	-0.074	-0.064	0.021	0.313

Binary logistic regression. *= Significant.

Out of the 184 LN patients who had their 1st biopsy, 77 patients (41.8%) had a 2nd biopsy. The findings in the 2nd biopsy did not show any difference as regards the class of LN, but the mean value of activity index was statistically significantly lower in the 2nd biopsy compared to 1st biopsy, while the mean value of chronicity index was statistically significantly higher in the 2nd biopsy compared to the 1st biopsy (Table 5).

Table (5): Comparison between the 1st and 2nd renal biopsies in the studied LN patients (n=184)

Variables	1st Biopsy (n=184)	2nd Biopsy (n=77)	Test of Significance	P-Value
LN Class: No (%). Class III: Class IV:	67 (36.4%) 117 (63.5%)	33 (42.8%) 44 (57.1%)	X^2=0.95	0.33
Activity index (AI) mean±SD	10.0±4.4	7.4±4.2	t=-4.41	**<0.0001***
Chronicity index (CI) mean±SD	2.4±1.6	3.0±2.3	t=2.41	**0.016***

X^2= Chi-square test. t= student t-test. *= Significant.

Moreover, out of 57 patients with LN, almost 31% needed re-induction therapy, and within this group, 24.6% received CYC, while 75.4% received MMF for re-induction. The two groups had significant differences in various factors such as the cause of re-induction, serum creatinine levels, primary and maintenance therapy, remission, biopsy, induction, and withdrawal from immunosuppression (Table 6).

In 35 patients of these 57 patients (61.4%), re-induction therapy was administered after a 2nd biopsy due to a deterioration in kidney condition, while 22 patients (38.6%) did not respond to initial induction therapy. The CYC re-induction group had statistically significantly higher serum creatinine levels compared to the MMF re-induction group. However, there was no significant difference between the two groups in terms of 24-hour urinary protein levels (Table 6).

Out of the 57 patients with LN who underwent re-induction therapy, 75.4% received MMF and 24.6% received CYC. Of those who received CYC for re-induction, 71.4% had previously received CYC for 1ry induction, while 28.6% had received MMF. For 1ry maintenance, 42.8% received MMF and 57.2% received AZA. Among those who received MMF for re-induction, 86% had previously received CYC for 1ry induction, while 14% had received MMF. For 1ry maintenance, 34.9% received MMF and 65.1% received AZA (Table 6).

In the case of the 14 patients who underwent re-induction with CYC, 64.3% were prescribed maintenance therapy with MMF, while 21.4% received AZA and 14.3% were not given any maintenance therapy. Of these patients, 78.6% achieved a 2nd remission, but 21.4% did not and required a 3rd biopsy. In the case of the 43 patients who underwent re-induction with MMF, 93% received maintenance therapy with AZA, and 7% received MMF. A 2nd remission was achieved by 92.9% of these patients, but 7.1% did not and required a 3rd biopsy (Table 6).

In the CYC group, out of three patients who were supposed to receive the 3rd induction, one was given CYC, one was given MMF, and one did not receive any 3rd induction. In the MMF group, out of three LN patients, one was given CYC, and two did not receive the 3rd induction. In addition, one patient from the CYC group and two patients from the MMF group withdrew from immunosuppression (Table 6).

Table (6): Comparison between CYC and MMF re-induction groups as regards re-biopsy, laboratory data, and outcome

Variables	CYC re-induction (14 patients)	MMF re-induction (43 patients)	Test of significance	P-value
Cause of re-induction: **-Worsening (biopsy-based) (2^{nd} biopsy)** **-No-response**	12 (85.7%) 2 (14.3%)	23 (53.5%) 20 (46.5%)	X^2= 29.3	**<0.0001***
S. creatinine (mg/dL) mean±SD	3.2±0.75	1.5±0.36	t= 2.8	**0.007***
Urinary proteins (g/day) mean±SD	5.08±1.18	4.7±1.16	t= 0.35	0.724
1ry induction No. (%): CYC **MMF**	10 (71.4%) 4 (28.6%)	37 (86%) 6 (14%)	X^2= 5.7	0.06
1ry maintenance No. (%): MMF **AZA**	6 (42.8%) 8 (57.2%)	15 (34.9%) 28 (65.1%)	X^2= 29.3	**<0.0001***
Maintenance after re-induction No. (%) **No** **MMF** **AZA**	2 (14.3%) 9 (64.3%) 3 (21.4%)	0 3 (7%) 40 (93%)	49.13	**<0.001***
2^{nd} remission No. (%)	11 (78.6%)	40 (92.9%)	8.45	**0.015***
No remission No. (%)	3 (21.4%)	3 (7.1%)	8.45	**0.015***
Need for 3^{rd} biopsy No. (%)	3 (21.4%)	3 (7.1%)	8.45	**0.015***
3^{rd} induction No. (%) **No** **CYC** **MMF**	1 (0.8%) 1 (0.8%) 1 (0.8%)	2 (4.6%) 1 (2.3%) 0	8.45	**0.016***
Withdrawal of immunosuppression No. (%)	1 (0.8%)	2 (4.6%)	8.45	**0.016***

X^2= Chi-square test. t= student t-test. *= Significant.

Out of the 132 patients diagnosed with LN, 71.7% were given CYC as their 1ry treatment, with 50% of them requiring a 2^{nd} biopsy. There was no noticeable difference in the LN classification between the 1^{st} and 2^{nd} biopsies, with similar percentages of class III and class IV. However, the activity index was statistically significantly lower in the 2^{nd} biopsy compared to the 1^{st} biopsy, while the chronicity index was statistically significantly higher. Also, out of the 52 patients diagnosed with LN, 28.3% were given MMF as their 1ry treatment, with 21.1% of them requiring a 2^{nd} biopsy. There was no noticeable difference in the LN classification, activity, or chronicity indices between the 1^{st} and 2^{nd} biopsies (Table 7).

Table (7): Comparison between 1^{st} and 2^{nd} biopsies in CYC and MMF 1ry induction groups in studied LN patients

CYC induction (66 patients)	1^{st} biopsy (n=66)	2^{nd} biopsy (n=66)	Test of significance	P-value
Class of LN				
• **III**	28 (42.4%)	32 (48.4%)	X^2=0.21	0.64
• **IV**	38 (57.6%)	34 (51.6%)	X^2=0.25	0.61
Activity index (AI) (mean±SD)	10.6 ±4.08	6.83 ±4.02	t=-5.34	**0.001***
Chronicity index (CI) (mean±SD)	2.5 ±1.2	3.4 ±1.4	t=3.9	**0.04***
MMF 1ry induction (11 patients)	**1^{st} biopsy**	**2^{nd} biopsy**	**Test of significance**	**P-value**
Class of LN				
• **III**	1 (9.1%)	2 (18.2%)	X^2=0.02	0.86
• **IV**	10 (90.9%)	9 (81.8%)	X^2=0.32	0.58
Activity index (AI) (mean±SD)	12.4±4.08	9.9±4.7	t=-1.3	0.19
Chronicity index (CI) (mean±SD)	2.4± 1.1	2.7±1.3	t=0.58	0.56

X^2= Chi-square test. t=Paired t-test. *= Significant.

Seventy-seven patients (41.8%) out of the 184 LN patients had a 2nd renal biopsy; (85.7%) of patients had received CYC 1ry induction (66) patients, and (14.3%) of patients had received MMF 1ry induction (11 patients). Most of them (62 patients) (80.5%) had a 2nd biopsy after 6 months of 1ry induction therapy, while the remaining (15 patients) (19.5%) had an event-based 2nd biopsy. In the 2nd biopsy, a statistically significantly higher percentage in the MMF 1ry induction group had class IV LN than the CYC group, while a statistically significantly higher percentage of the CYC 1ry induction group had class III LN than the MMF group (Table 8). Also, in the 2nd biopsy, the CYC 1ry induction group had a statistically significantly lower activity index mean±SD than the MMF group and a statistically significantly higher chronicity index mean±SD in the CYC group than the MMF group. Among LN patients (77 patients) who had a 2nd biopsy, 35 patients of them received re-induction (45.4%), most of them (23 patients) (65.7%) received MMF for re-induction, versus (12 patients) (34.3%) received MMF for re-induction (Table 8).

Table (8): Comparison of the results of 2nd renal biopsy in the CYC versus MMF 1ry induction

Variables	CYC induction (66 patients)	MMF induction 11 patients	Test of Significance	P-value
Timing of 2nd biopsy: Event-based 6-months of induction therapy	13 (19.69%) 53 (80.31%)	2 (18.18%) 9 (81.81%)	X^2= 0.014	0.9
Lupus nephritis (LN) class: Class III Class IV	31 (46.9%) 35 (53.1%)	2 (18.2%) 9 (81.8%)	X^2= 12.4	**0.006 ***
Activity index (AI) mean±SD	7.03±3.3	9.9±4.7	t= 2.5	**0.04***
Chronicity index (CI) mean±SD	3.1±1.5	2.7±1.1	t= 2.5	**0.04***
Re-induction	29 (43.9%)	6 (54.5%)	0.27	0.6
No induction	37 (56.1%)	5 (45.5%)	0.42	0.5
Type of-re-induction: CYC MMF	7 (10.6%) 22 (33.33%)	5 (45.45%) 1 (9.09%)	7.73	**0.03***

X^2= Chi-square test. t= student t-test. *= Significant.

DISCUSSION

Aggressive treatment is necessary for achieving remission in patients with class III and IV proliferative LN to prevent kidney damage [13]. A repeated renal biopsy with an activity index (AI) score greater than 3 predicts relapse, while a chronicity index (CI) score greater than 3 predicts long-term renal impairment [14]. This retrospective cohort study included 184 Egyptian female patients with systemic lupus erythematosus (SLE) and proliferative LN (class III and IV) who received treatment at the Urology and Nephrology Center at Mansoura University in Egypt from January 2002 to December 2020.

Following the primary induction therapy, remission was achieved in 86 patients (46.7%), while 98 patients (53.3%) did not experience remission. Those who achieved remission had a lower chronicity index (CI) compared to those who did not respond. According to **Wang *et al.*** [15] patients with class IV LN face the greatest risk of progressing to end-stage renal disease (ESRD), with 15-30% failing to reach remission and a similar percentage experiencing a relapse after achieving remission.

The use of MMF for primary induction in LN patients resulted in a significantly higher remission rate of 71.15% compared to the remission rate of 31.12% in patients who received CYC. This finding is consistent with the research conducted by **Jiang *et al.*** [16], which showed that MMF was more effective than CYC in achieving complete remission and improving serum complement C3 levels during primary induction therapy for LN. The type of induction therapy and activity index were identified as predictors for non-remission. In a study by **Malvar *et al.*** [17], it was reported that 30% of LN patients who attained clinical remission after induction treatment had an activity index of 5 or higher during repeated renal biopsies.

In terms of primary maintenance therapy, patients who were on AZA had a higher rate of non-remission compared to those who were on MMF. Additionally, **Lee and Song** [18] discovered that using tacrolimus and MMF as maintenance therapy for LN patients resulted in a lower rate of renal relapse compared to using AZA and CYC.

Out of the 184 patients with LN, 41.8% needed a second biopsy, and 30.9% required re-induction. A higher percentage of patients who received CYC 1ry induction needed a second biopsy (50%) and re-induction (35.6%) compared to those who received MMF (21.2% and 19.23%). This finding supports the conclusion of **Al-Nahal *et al.*** [19] that MMF is more effective than CYC in achieving remission in LN patients during 1ry induction.

Patients with LN who were treated with CYC for primary induction showed a decrease in activity index and an increase in chronicity index in the second biopsy compared to the first biopsy. Conversely, patients who received MMF for primary induction did not show any difference between the first and second biopsies. This finding aligns with the observation made by **Moroni *et al.*** [11] that 72% of LN patients demonstrated an increase in chronicity index during a repeated renal biopsy and that CYC can provide protection against such an increase.

After the primary induction, serum creatinine was lower in the MMF group than in the CYC group, but the 24-hour urinary proteins did not differ. This agrees with **Tunnicliffe *et al.* [20],** who found that MMF was associated with a higher rate of induction of complete disease remission and preserve kidney function at 6 months compared to CYC.

Among the 57 LN patients who received re-induction, 75.4% received MMF with a secondary remission in 92.9%, and 24.6% received CYC with a secondary remission in 78.6%. **Gasparotto *et al.* [21]** advised that in the non-responding or refractory LN patients, it is better to switch to another 1st line treatment; MMF, CYC, calcineurin inhibitors (CNI) as mono or multitherapy, or the use of rituximab (RTX).

When it came to patients needing a second biopsy, the majority (80.5%) received it after completing their initial induction therapy, while the rest (19.5%) had a second biopsy due to declining renal function. This aligns with research by **Sánchez-Cubías *et al.* [22],** which identified relapse, lack of response, and post-therapy as the primary reasons for repeated kidney biopsies (with relapse accounting for 44-78% and lack of response for 13-51%).

In the activity index (AI) pathological changes include fibrinoid necrosis, cellular crescents, endocapillary hypercellularity, and interstitial inflammation, while in the chronicity index (CI) pathological changes include fibrous crescents, segmental sclerosis, interstitial fibrosis, and tubular atrophy. The AI indicates the need for more aggressive treatment, while the CI indicates a poor prognosis [23].

Complete remission (CR) is defined as the return of serum creatinine back to the baseline level, and a decrease in the urinary albumin/creatinine ratio to <500 mg/g, while partial remission (PR) is defined as stabilization, or improvement of serum creatinine, but not to normal, and a ≥50% decrease in the albumin/creatinine ratio [24].

Genetic factors play an important role in the risk of developing LN in SLE patients of different ethnicities, and the response to treatment differs as well. Hispanic, African American, and Asian patients develop more severe SLE, and LN, than patients of European descent [25].

A research study conducted by **Momtaz *and colleagues*[26]** at Cairo University focused on Egyptian patients with SLE. The study discovered that 72.7% of patients with LN achieved remission when given CYC for induction, while 67.3% of patients in the MMF group achieved remission but had a lower rate of LN flare. Additionally, the presence of CKD was linked to class IV LN, high CI, crescents, and interstitial fibrosis in the biopsy, according to the study.

In the current study, the use of MMF for secondary maintenance after CYC re-induction achieved a secondary remission in 78.6% of patients, while the use of AZA for secondary maintenance after MMF re-induction achieved a secondary remission in 93% of patients. A third biopsy was required in 21.4% of the CYC re-induction group versus 7.1% of the MM re-induction group. **Deng *et al.* [27]** found that the MMF is more effective than the AZA as a maintenance therapy for LN with a lower risk of leukopenia.

In this study, it was found that Egyptian female patients with lupus nephritis and systemic lupus erythematosus had better remission rates after receiving primary induction therapy with mycophenolate mofetil compared to cyclophosphamide. Additionally, patients with lower activity index scores were more likely to experience remission, and those who received mycophenolate mofetil for primary maintenance had higher remission rates than those who received azathioprine. Furthermore, the chronicity index was lower in patients who experienced remission.

Out of the 184 LN patients who had their 1st biopsy, 77 patients (41.8%) had a second biopsy. The findings in the 2nd biopsy did not show any difference as regards the class of LN, but the activity index was lower and the chronicity index was higher in the second biopsy, compared to the first biopsy.

A higher percentage of LN patients required a second biopsy after CYC primary induction than after MMF, and the second biopsy in the CYC group showed a lower activity index but a higher chronicity index than the first biopsy, while no difference was found in the MMF group. Also, no difference was found as regards the LN class between the first and second biopsies.

In comparison to CYC, the primary induction with MMF resulted in lower serum creatinine levels but had no significant impact on proteinuria, and re-induction with MMF showed a higher remission rate than CYC. In most cases, the second biopsy was conducted after the completion of the first induction, while in some cases, it was an event-based biopsy. Using MMF for secondary maintenance yielded a higher remission rate than AZA, and a larger proportion of LN patients required a third biopsy after re-induction with CYC compared to MMF.

Points of strength:

The focus of this research was on women in Egypt who had systemic lupus erythematosus and proliferative lupus nephritis. The study examined how these patients responded to primary induction therapy using either CYC or MMF, and whether they required a second or even a third biopsy. Additionally, this research analyzed the differences between repeated biopsies, including the class, activity, and chronicity indices of lupus nephritis.

Limitations of the study:

It represents a single-center experience and did not compare various centers.

CONCLUSIONS

Repeated renal biopsies are important in the follow-up of Egyptian female patients with proliferative LN, after 1ry induction therapy or an event-based biopsy. The use of MMF reduces the risk for non-remission, and the need for re-biopsy, or re-induction.

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