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Evaluating Tubuloglomerular Outcome by Measuring Proteinuria and Neutrophil Gelatinase Associated Lipocalin after Induction of Low-Dose Cyclophosphamide among Patients with Class III/IV Lupus Nephritis

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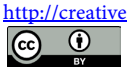
Abstract

Background: In lupus nephritis (LN), glomerular dysfunction is evident by proteinuria. Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) has emerged as a promising biomarker to detect tubular dysfunction. **Objective:** To evaluate the tubulo-glomerular outcome after induction of Euro-Lupus regimen by measuring proteinuria and NGAL. **Methods:** This was a quasi-experimental study. Patients were included based on American College of Rheumatology (ACR) criteria. A total of 19 diagnosed lupus nephritis (class III & IV with or without class V) cases were evaluated. Their renal biopsy report was labelled according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS). All patients were treated with low-dose cyclophosphamide (Euro-Lupus regimen) for three months. Patients were assessed at baseline and then monthly up to 3 months of induction. The observed major variables were complete blood count (CBC), lupus serology (ANA, anti-dsDNA, C3, C4, anti-phospholipid), 24-hour urinary total protein (UTP), spot urinary protein creatinine ratio (PCR), spot urinary NGAL, urinary NGAL creatinine ratio, serum creatinine, serum albumin and estimated glomerular



filtration rate (e-GFR). The activity index (AI), chronicity index (CI) and disease activity over time (SLEDAI) were assessed accordingly. **Results:** Mean age of the study population was 29 ± 10 years, where 95.5% were female. After 3 months of induction with low-dose cyclophosphamide (Euro-Lupus regimen), hemoglobin, eGFR, and serum albumin level had significantly increased from baseline ($p < 0.05$), while serum creatinine, UTP, PCR, urinary NGAL and disease activity score were significantly decreased ($p < 0.05$). Complete response was seen in 26.3% study patients and partial response in 36.8% patients after 3 months of induction. Response did not differ significantly in this short period of treatment among different histological types of LN. **Conclusion:** Induction in lupus nephritis by low-dose cyclophosphamide (Euro-Lupus regimen) reduces proteinuria and urinary NGAL significantly after three months of therapy. This regimen is effective in improving glomerular and tubular dysfunctions of LN.

Keywords

Euro-Lupus Regimen, Lupus Nephritis (LN), Neutrophil Gelatinase Associated Lipocalin (NGAL), Proteinuria, Tubulo-Glomerular Outcome

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects almost every organ system in the body, most commonly the skin, kidneys, brain and joints. Renal involvement in SLE, lupus nephritis (LN), is extremely diverse, ranging from asymptomatic urinary findings to fulminant renal failure or florid nephrotic syndrome [1]. Lupus nephritis (LN) is a major cause of morbidity and mortality and occurring in approximately 35% to 50% of patients with SLE [2]. All four renal compartments—glomeruli, tubules, interstitium and blood vessels may be affected in LN [3]. The incidence of renal involvement varies with ethnicity; Caucasians (European, European Americans; 12% - 33%) are less likely to have LN than black (African American, Afro-Caribbean; 40% - 69%), Hispanic (36% - 61%), or Asian (Indian, Chinese; 47% - 53%) patients [4] [5]. The peak incidence of lupus is 15 - 45 years of age, with women outnumbering men by 9:1 [5]. So, most of the lupus patients are women of childbearing age. LN is a relapsing condition and relapses are associated with development of chronic kidney disease (CKD). Forty percent of complete responders experienced a kidney relapse within a median of 41 months after remission, and 63% of partial responders had a kidney flare within a median of 11.5 months after response [6]. However, 8% to 15% of patients with LN progress to end-stage renal disease (ESRD) [7].

Management of lupus nephritis requires a timely and coordinated use of immunosuppressive therapy. The aim of management of LN is to achieve the best possible clinical efficacy with renal remission and minimal toxicity of the immunosuppressive agents [3]. Cyclophosphamide (CYC) has been established as a traditional standard treatment of LN based on studies in the 1970s and 1980s at the

National Institute of Health (NIH) [8] [9]. The major limitation of the use of cyclophosphamide in lupus nephritis is its untoward side effects, which include infection, ovarian and bladder toxicities, leukopenia and an increased risk of malignancy [10]. Some of these toxicities are dose-dependent. In patients with SLE, a higher cumulative dose of cyclophosphamide and older age was associated with an increased risk of premature ovarian failure after cyclophosphamide administration [11]. The Euro-Lupus Nephritis Trial (ELNT) demonstrated a comparable efficacy and safety profile of low-dose CYC to the high dose NIH regimen [8]. The Euro-Lupus regimen consists of lower dose of intravenous CYC for a short period of time (cumulative dose 3 gm) as a remission-inducing agent.

Proteinuria is one of the best available biomarkers for assessing kidney involvement in SLE and for monitoring response to therapy and progression of the disease [12]. Accurate quantification of the proteinuria is essential to define the partial and complete remission of lupus nephritis in research studies and clinical trials.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kd protein secreted by leukocytes and tubular epithelial cells in response to conditions like stress and inflammation [13]. NGAL is synthesized within the distal nephron and secreted into urine from the loop of Henle's ascending limb to the collecting ducts, primarily from the distal nephron [14]. This small protein, readily detectable in urine, emerges as an early and sensitive biomarker of acute kidney injury (AKI) [13] [14]. In addition to proteinuria, NGAL has emerged as an important biomarker to detect disease activity and renal outcome and performs better than conventional markers such as anti-double-stranded DNA (anti-dsDNA), complements (C3 and C4) in predicting a clinical response to therapy of active lupus nephritis [14]. Some studies have shown that the concentration of urinary NGAL represented a very sensitive and highly predictive biomarker for progressive tubular injury. NGAL responds earlier than other renal status markers. NGAL level serves as an early indicator of acute kidney injury (AKI) in many acute clinical situations [15]-[18]. Further studies should be focused on determining whether NGAL can be used in clinical practice with greater sensitivity and specificity to predict long-term outcomes for SLE patients. In this background current study aimed to evaluate the tubuloglomerular outcome of lupus nephritis after induction with low-dose cyclophosphamide (Euro-Lupus regimen) by measuring proteinuria and urinary NGAL.

2. Methodology

This quasi-experimental study was conducted at Department of Nephrology, National Institute of Kidney Disease and Urology (NIKDU), Dhaka, Bangladesh from March 2022 to August 2023. A total of 22 diagnosed lupus nephritis (class III & IV with or without class V) cases were enrolled following purposive sampling technique. Adult (age ≥ 18 years) patients of both sexes newly diagnosed biopsy proven active/active + chronic class III/IV lupus nephritis (with/without class V) were included. Patients of neurological or pulmonary lupus, patients with active infection or active malignancy, lupus patient prior treatment with cyclophospha-

mide, subjects hypersensitive to cyclophosphamide and pregnant or lactating women were excluded from the study.

Study procedure

Before starting the study, formal approval was taken from Research Review Committee (RRC) of the Department of Nephrology, NIKDU, Dhaka, Bangladesh. Then, formal ethical approval was taken from the Ethical Review Committee (ERC) of NIKDU, Dhaka, Bangladesh. Prior to enrollment, the objectives, procedure and risk/benefit of the study were explained and an informed written consent was taken from each participant. All study patients (LN) were assessed and diagnosed on the basis of ACR criteria. A complete case history and relevant physical examination findings were recorded. Their renal histology reports were classified according to the International Society of Nephrology/Renal Pathology Society [19]. SLE with renal involvement, which is the case definition of lupus nephritis, was retrieved from "American College of Rheumatology (ACR)" Guidelines for screening, treatment, and management of Lupus Nephritis [20]. All patients were treated with Intravenous (IV) Cyclophosphamide 500 mg every 2 weeks for 3 months and IV methylprednisolone 500 mg daily for 3 days followed by oral prednisolone 1 mg/kg/day (maximum 80 mg/day) for 2 weeks then tapered by 5 mg every 2 weeks interval to 5 - 7.5 mg/day over 6 months. Supportive therapy with Hydroxychloroquine 6.5 mg/kg/day (adjusted for eGFR) and angiotensin receptor blocker (ARB)-Losartan Potassium 50 mg/day was given. Duration of induction phase was 3 months. The side effects of cyclophosphamide were monitored carefully. Efforts were taken to decrease the effect of confounding variables and to reduce the likelihood of important errors that compromise the essential integrity of the research data.

Prior to initiating treatment, baseline values of complete blood count (CBC) with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum alanine transaminase (ALT), serum albumin, serum creatinine, serum levels of complement components (C3/C4), antinuclear antibody (ANA), serum anti-ds DNA antibody (Anti-ds DNA), urine routine microscopic examination (urine-R/M/E), 24 hours urinary total protein (UTP), spot urinary protein creatinine ratio (PCR), urinary NGAL, urinary NGAL creatinine ratio and estimated glomerular filtration rate (e-GFR) in each study participant were measured following standard procedure. After three months of treatment, these tests were repeated accordingly. Before and after therapy, renal disease activity in each patient was evaluated using the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)—Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), which is SELENA-SLEDAI score [21].

Proteinuria

Proteinuria is defined as an abnormal excretion of protein in urine of more than 150 mg/day [12].

Definition of renal response to therapy in LN based on KDIGO guideline [21]

Complete response

- Reduction in proteinuria < 0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection.
- Stabilization or improvement in kidney function (±10% - 15% of baseline).
- Within 6 - 12 months of starting therapy, but could take more than 12 months.

Partial response

- Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection.
- Stabilization or improvement in kidney function (±10% - 15% of baseline).
- Within 6 - 12 months of starting therapy, but could take more than 12 months.

No response

- Failure to achieve a partial or complete response within 6 - 12 months of starting therapy.

Urinary NGAL assay

Early morning urine sample was collected and then centrifuged at 3000 rpm for 5 minutes, aliquoted and stored in a refrigerator at −20˚C until analysis. Urinary NGAL was measured by ELISA method using a commercially available Human NGAL/Lipocalin 2 ELISA kit (BioVendor: Detection limit = 0.02 ng/mL; Intra-assay CV = 5.3%).

Statistical analysis

Following data collection, the collected data assessed for completeness, accuracy and consistency before analysis was commenced. Statistical analysis was performed by using windows-based computer software Statistical Packages for Social Sciences (SPSS) version 26. Quantitative data were expressed as mean with standard deviation (SD) and qualitative data were expressed as frequency with percentage. Paired-t-test, ANOVA and chi-square tests were performed to analyze normally distributed data according to applicability. A p-value < 0.05 was considered as statistically significant.

3. Results

This hospital-based quasi-experimental study was conducted on a total of 22 patients [diagnosed case of class III and IV lupus nephritis (with or without class V)]. This study had collected baseline data of 22 patients, but after 3 months of induction, 2 patients had died during this study period, and 1 had been lost to follow-up. Therefore, data from 19 lupus patients were finally analyzed.

The mean age of the patients was 29 ± 10.7 years, majority of the patients were female (94.8%). The mean BMI of the patients was 23 ± 3 kg/m^2, more than half (52.6%) of the patients were between 20 to 29 years age. The mean duration of SLE and lupus nephritis was 26 ± 12 months and 3 ± 2 months, respectively (Table 1). Among the study patients, the most common (over seventy percent) clinical symptoms were arthritis, followed by photosensitivity, oral ulcer and malar rash. Almost half of the study patients had non-scarring alopecia (Table 1). According to baseline lupus serology, all (100%) study patients had positive ANA titer and 94.8% had positive anti-ds DNA. Most of the patients (89.5%) had low C3 level; whereas, about half of patients had low C4 level. Anti-phospholipid antibody was

tested positive among only 3 study patients (Table 1). Based on renal biopsy, 11(57.9%) patients had class IV LN. Among rest, 4 (21.1%) had class III LN and 4 (21.1%) had class IV + V LN (Table 1).

Table 1. Baseline characteristics of the lupus nephritis patients (N = 19).

Variables	Number (%)	Mean ± SD
Mean ± SD age (year)		29 ± 10.7
Age groups (years)		
<20	2 (10.5)	
20 - 29	10 (52.6)	
30 - 39	5 (26.4)	
≥40	2 (10.5)	
Gender		
Male	1 (5.2)	
Female	18 (94.8)	
BMI (kg/m²)		23 ± 3
SLE Duration (months)		26 ± 12
LN Duration (months)		3 ± 2
Symptoms*		
Arthritis	15 (78.9)	
Photosensitivity	14 (73.7)	
Oral ulcer	14 (73.7)	
Malar rash	14 (73.7)	
Non scaring alopecia	10 (52.6)	
Fever	4 (21.1)	
Serology*		
ANA		
Positive	19 (100.0)	
Negative	0 (0.0)	
Anti-ds DNA		
Positive	18 (94.8)	
Negative	1 (5.2)	
C3		
Normal	2 (10.5)	
Low	17 (89.5)	
C4		
Normal	9 (47.4)	
Low	10 (52.6)	
Anti-Phospholipid antibody		
Positive	3 (15.8)	
Negative	16 (84.2)	
Classes of lupus nephritis		
Class III	4 (21.1)	
Class IV	11 (57.9)	
Class IV+ Class V	4 (21.1)	

*Multiple response.

It was observed that important laboratory parameters, such as hemoglobin (Hb), eGFR, serum albumin and levels had significantly increased after 3 months of induction ($p < 0.05$). On the other side, serum creatinine, 24 hours UTP, spot urinary PCR, urinary NGAL, urinary NGAL creatinine ratio and SLEDAI score were significantly decreased after 3 months of induction ($p < 0.05$) (Table 2).

Table 2. Comparison of laboratory parameters baseline with these 3 months after induction among the lupus nephritis patients (N = 19).

Variables	Baseline (n = 19)	After 3 months (n = 19)	p value*
Hemoglobin (g/dL)	10.1 ± 1.1	11.2 ± 1	0.029[s]
S. creatinine (mg/dL)	1.5 ± 0.62	1 ± 0.4	0.005[s]
eGFR (mL/min/1.73m^2)	60 ± 22.5	81 ± 31.3	0.023[s]
S. Albumin (g/dL)	2.9 ± 0.6	3.7 ± 0.5	0.001[s]
UTP (g/day)	3.03 ± 0.93	1.55 ± 0.62	0.001[s]
Spot urinary PCR	3.46 ± 1.28	1.64 ± 0.61	0.001[s]
SLEDAI	20.5 ± 5.6	9.1 ± 4.4	0.001[s]
Urinary NGAL (ng/mL)	15.8 ± 6.3	11.4 ± 4.8	0.021[s]
Urinary NGAL creatinine ratio (ng/mg)	34.8 ± 10.36	28.3 ± 8.3	0.039[s]

Data were expressed as mean ± SD, *p value was determined by Paired t test, s = significant.

After 3 months of induction among 19 patients, 5 (26.3%) patients had a complete response and 7 (36.8%) patients had a partial response. However, 7 (36.8%) patients had no response to drug therapy (Figure 1).

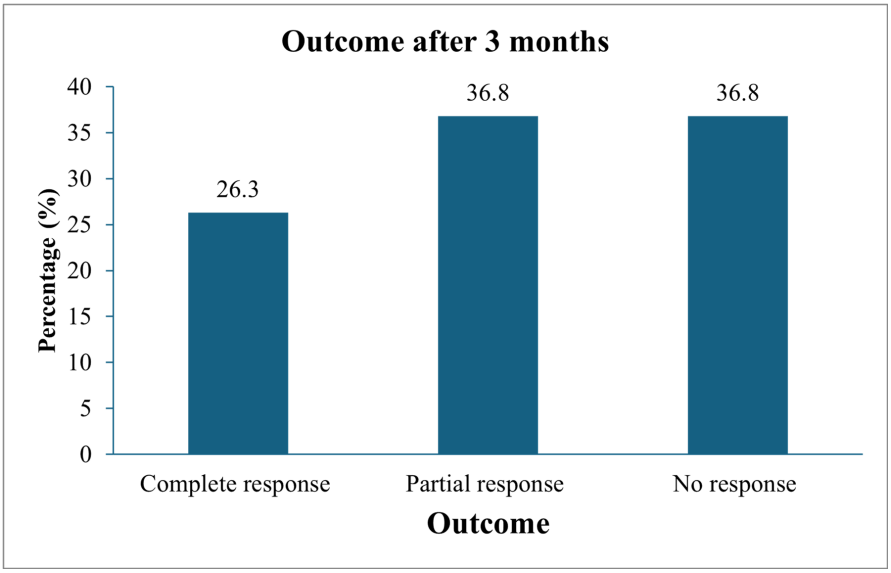


Figure 1. Outcome of the lupus nephritis patients after 3 months of induction (N = 19).

Analysis of baseline parameters prior to induction showed; mean 24-hour UTP and spot urinary PCR were significantly low in complete response patients com-

pared to partial response patients and no-response patients ($p < 0.05$). Renal function was comparatively well preserved in complete response patients than partial response patients and no-response patients. Similar trends were observed in SLEDAI, activity indices and chronicity indices. Serum albumin level was significantly high in complete response patients than partial response patients and no-response patients ($p < 0.05$). Urinary NGAL and urinary NGAL creatinine ratio were also significantly low in complete response patients than partial response patients and no-response patients ($p < 0.05$) (Table 3).

Table 3. Comparison of baseline parameters between three response group prior to induction (N = 19).

Variables	Complete response (n = 5)	Partial response (n = 7)	No-response (n = 7)	p value*
Hemoglobin (g/dL)	10.8 ± 0.7	9.7 ± 1.4	10 ± 1.1	0.250
Serum creatinine (mg/dL)	0.9 ± 0.31	1.7 ± 0.62	1.8 ± 0.86	0.077
eGFR (mL/min/1.73m^2)	76 ± 13.6	57 ± 19.9	53 ± 17.6	0.097
Serum albumin (g/dL)	3.6 ± 0.5	3 ± 0.2	2.5 ± 0.5	0.001^s
UTP (g/24hour)	1.3 ± 0.2	2.8 ± 0.5	4.4 ± 1.4	0.001^s
Spot urinary PCR	1.4 ± 0.2	3.2 ± 0.7	5.2 ± 2.8	0.007^s
Urinary NGAL (ng/mL)	5.1 ± 1.8	12.2 ± 4.4	26.9 ± 11.3	0.001^s
Urinary NGAL creatinine ratio (ng/mg)	15 ± 6.3	23.9 ± 11.4	59.8 ± 23.6	0.001^s
SLEDAI	18.4 ± 7.1	20.1 ± 3.3	22.6 ± 6.7	0.484
Activity indices	7.2 ± 2.6	9 ± 4.1	9.8 ± 3.9	0.959
Chronicity indices	2.8 ± 1.2	3 ± 1.2	3.1 ± 1.2	0.912

Data were expressed as mean ± SD, *p-value was determined by One-way ANOVA test, s = significant.

Again after 3 months of induction parameters like- 24 hours UTP, spot urinary PCR, urinary NGAL, urinary NGAL creatinine ratio and SLEDAI were significantly low in complete response patients compared to partial response patients and no-response patients ($p < 0.05$). But serum albumin level after 3 months was significantly high among complete response patients compared to partial response patients and no-response patients ($p = 0.011$). Serum creatinine and eGFR levels after 3 months of induction were significantly changed among complete response patients compared to partial response patients and no-response patients ($p < 0.05$) (Table 4).

Table 4. Comparison of laboratory parameter of after 3 months of induction between three response group (n = 19).

Variables	Complete response (n = 5)	Partial response (n = 7)	No-response (n = 7)	p value*
Hb (g/dL)	11.3 ± 1	11 ± 1.4	10.5 ± 1.3	0.522
S. creatinine (mg/dL)	0.9 ± 0.2	1.7 ± 0.5	1.8 ± 0.6	0.023^s
eGFR (mL/min/1.73m^2)	76 ± 13.6	57 ± 16.9	53 ± 15.6	0.038^s

Continued

S. Albumin (g/dL)	3.9 ± 0.3	3.5 ± 0.4	3.2 ± 0.4	0.011[s]
UTP (g/day)	0.31 ± 0.16	1.21 ± 0.27	2.61 ± 1.06	0.001[s]
Spot urinary PCR	0.55 ± 0.14	1.76 ± 0.52	3.17 ± 0.9	0.001[s]
SLEDAI	4.0 ± 1.41	9.43 ± 2.76	12.33 ± 3.88	0.001[s]
Urinary NGAL (ng/mL)	6.69 ± 3.07	15.71 ± 5.43	26.97 ± 13.58	0.023[s]
Urinary NGAL creatinine ratio (ng/mg)	11.94 ± 4.96	27.11 ± 10.67	45.93 ± 19.75	0.042[s]

Data were expressed as mean ± SD, *p-value was determined by One-way ANOVA test, s = significant.

Regarding outcome after 3 months of induction, among class III LN patients (n = 4), 1 (25%) patient had complete response, another 1 (25%) patient had no response, but 2 (50%) patients had partial response, However, among class IV LN participants (n = 11); 5 (45.4%) patients had no response, but 3 (27.3%) patients had complete response and another 3 (27.3%) patients had partial response. In class IV+V LN participants (n = 4), 2 (50%) patients had a partial response, but 1 (25%) patient had a complete response, and another 1 (25%) patient had no response. Although, outcome after 3 months of induction had no significant association with renal biopsy classes (p = 0.999) (Table 5).

Table 5. Comparison of outcome after 3 months of induction among the patients with different classes of lupus nephritis (N = 19).

Variable	Classes of lupus nephritis			p value*
	Class III n (%)	Class IV n (%)	Class IV + V n (%)	
Complete	1 (25)	3 (27.3)	1 (25)	0.999[ns]
Partial	2 (50)	3 (27.3)	2 (50)	
No response	1 (25)	5 (45.4)	1 (25)	

*p value was determined by chi-square test, ns = not significant.

After 3 months of induction, only 1 (5.3%) patient had a relapse or flare of lupus nephritis (Table 6).

Table 6. Frequency of relapse or flare after 3 months of induction (N = 19).

Variables	Frequency	Percentage
Normal	18	94.7
Relapse/flare	1	5.3

According to the side effects during 3 months of induction, 2 (10.5%) patients had chest infection, 1 (5.3%) respondent had leucopenia, 1 (5.3%) patient had urinary tract infection and another 1 (5.3%) patient had herpes zoster, respectively (Figure 2).

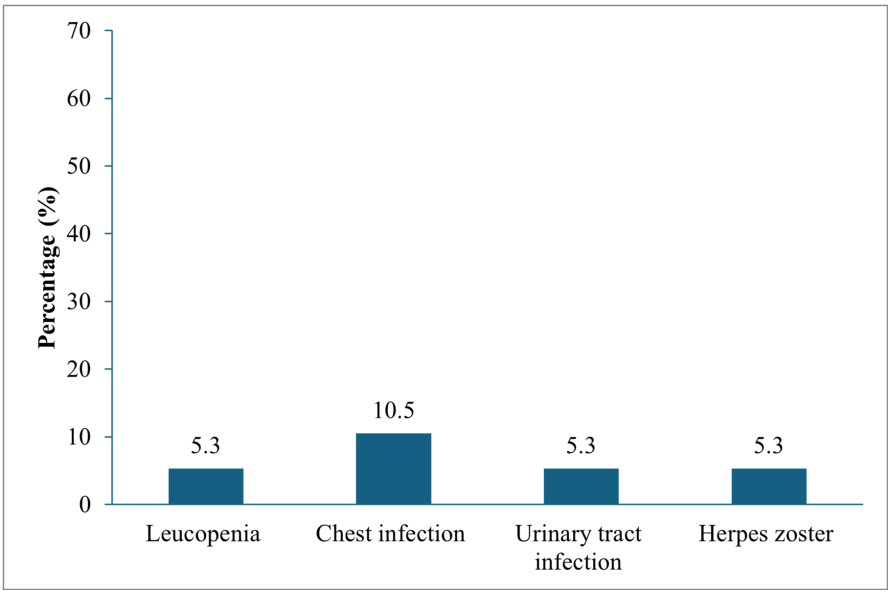


Figure 2. Complications observed during induction period (N = 19).

4. Discussion

Lupus nephritis (LN) is a severe form of systemic lupus erythematosus (SLE), which is often treated with a prolonged intravenous (IV) course of cyclophosphamide (CYC). A number of observational and randomized trials were conducted to identify the most effective and safe therapy for patients with LN. The Euro-Lupus Nephritis Trial (ELNT) compared six fortnightly injections of CYC with high-dose monthly injections; follow-up for 10 years showed that there were no differences in the outcome parameters or the side effects between high and low-dose intravenous CYC [22]. This current study was focused to evaluate tubuloglomerular outcome by measuring proteinuria and urinary NGAL after induction by low-dose CYC (Euro-lupus regimen) in Class III/IV Lupus nephritis.

In this study, the mean age of the study patients was 29 ± 10.7 years. Majority of the patients were female (94.8%). The mean BMI of the lupus patients was 23 ± 3 kg/m^2. More than half of the patients were in their third decade of life. The mean duration of SLE and lupus nephritis was 26 ± 12 months and 3 ± 2 months, respectively. The most common clinical symptoms were arthritis, followed by photosensitivity, oral ulcer, malar rash and non-scarring alopecia.

In this study, all lupus patients had positive ANA titer and 94.8% were tested positive anti-ds DNA. Of them, 89.5% had low C3 level, while about half of lupus patients had low C4 level. Anti-phospholipid antibody was tested positive among only 3 lupus patients.

According to renal histopathology, 57.9% patients had class IV LN. Among rest, 21.1% patients had class III LN and another 21.1% patients had class IV+V LN. These findings were consistent with related previous studies [8] [23] [24].

In this study, patients were categorized into complete, partial, and non-response groups. Notably, 36.8% of patients did not respond to treatment, highlighting the

challenges in managing lupus nephritis effectively. After 3 months of induction by Euro-lupus regimen, 26.3% participants had a complete response, and 36.8% had a partial response. These findings were supported by a related previous study, which showed that after 3 months of induction, 62% patients had achieved renal response with Euro-lupus regimen [8]. Another study compared rituximab, mycophenolate mofetil (MMF) and Euro-lupus regimen for induction therapy of active lupus nephritis patients; after 3 months of induction, they found 63.1% patients had achieved renal response in the CYC group [23]. High-dose CYC, low-dose CYC and MMF were compared among Egyptian populations, where at the end of the third month, 22.7% of patients had complete remission and 27.3% had partial remission in Euro-lupus group [24].

Although 36.8% participants had no response to therapy. Results of this study are comparable with a previous study where, in the low-dose arm, 43.9% achieved complete remission [25]. Nearly similar results were also found in the low-dose CYC arm in another study, where fifty percent of complete remission was observed [8]. Mehra *et al.* compared the efficacy of low-dose CYC versus high-dose CYC as induction therapy and they concluded that at the end of 24 weeks, there was no statistically significant difference in complete response and partial response in the low dose versus high dose [26].

The ELNT trial observed renal remission in 71% of the low dose and 54% of the high dose [8]. This was different from our study in respect to their definition of remission, end assessment at 41 months, most patients included did not have clinically severe kidney disease. Also, few Afro-American patients were included in ELNT trial and the outcome of lupus nephritis is poorer in those patients compared with Caucasian patients [27].

In this study, after 3 months of induction, it was found that 24-hour urinary protein and spot urinary protein-creatinine ratio, urinary NGAL and urinary NGAL creatinine ratio were significantly decreased. The disease activity in this study, as measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, also significantly improved with the treatment. Similar to this study, SLEDAI score decreased significantly in Euro-lupus regimen group in another study [24]. Moroni *et al.* showed that after 3 months of induction with Euro-lupus regimen proteinuria was significantly decreased from baseline [23]. The substantial decreases in serum creatinine, urinary protein levels and the SLEDAI scores indicate a reduction in disease activity following treatment. This suggests that the low dose CYC treatment is effective in controlling lupus nephritis.

Recently, some studies reported that high levels of urinary NGAL were found in SLE patients with nephritis, urinary NGAL may also be a predictor of flare-ups and the progression of LN disease activity [13] [14]. The results of this current study also revealed that the patients with active LN who did not respond to induction therapy had the highest baseline urinary NGAL levels, suggesting that urinary NGAL is a predictor for treatment response.

According to renal biopsy, about sixty percent of participants had class IV LN.

But outcome after 3 months of induction showed no significant difference of results in all renal biopsy classes. Another study showed that 54 % patients had class IV nephritis and the biopsy classes of LN did not influence the remission [25].

Monitoring for relapse or flare is critical in the management of lupus nephritis, and in this study, only 1 (5.3%) patient had relapse or flare. In a previous study, after 12 months of CYC treatment, 3 patients with lupus nephritis had relapse or flare again [28].

Notable adverse events observed in a study were there was a need for dialysis, re-admission, leucopenia and acute kidney injury [25]. Infection and leukopenia have always been major limiting factor in lupus therapy. In this current study, 21.1% of the total patients had infections that were consistent with a couple of related studies [9] [22] [29].

5. Conclusion

This study concluded that the Euro-lupus regimen provides complete remission in 26.3 % and partial remission in 36.8 % lupus cases. Induction by low-dose cyclophosphamide (Euro-lupus regimen) in lupus nephritis improves glomerular function which is as evident by reduction in proteinuria and tubular function as evident by decrease in urinary NGAL excretion. A nephrotic range proteinuria and a very high urinary NGAL excretion are bad prognostic factors for response to therapy. Response to induction therapy may not vary with different histological lupus classes.

Limitations of the study

This study has several limitations. It was a single center study with having small sample size. Moreover, this study did not compare efficacy and safety with other induction regimens of lupus nephritis.

Recommendations

Further multicenter studies with larger sample size are recommended.

Conflicts of Interest

All authors declared that they have no conflicts of interest.

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