SHORT-TERM OUTCOME OF PROLIFERATIVE LUPUS NEPHRITIS A SINGLE CENTER STUDY

JAWAD IBRAHIM RASHEED¹, BASHAR ABED MOUSA² &
HASANAIN MOHAMMED ALI MAKKI³

¹Consultant Nephrologist, Medical City-Baghdad Teaching Hospital, Baghdad, Iraq

²Specialist Nephrologist, Medical City, Baghdad, Iraq.

³Medical City-Baghdad Teaching Hospital, Baghdad, Iraq

ABSTRACT

Background

Systemic lupus erythematosus (SLE) is a chronic, multisystem and auto immune disorder. It is an unpredictable disease, which is also episodic in nature. The serious complication of SLE is Lupus Nephritis (LN) that is an inflammation of kidney. A study was conducted from a single center in Bhagdad to determine the epidemiological profile, clinical features, and short term outcomes in patients that suffer with lupus nephritis.

Patients and Methods

For this study, a total of 43 patients belonging to III/IV lupus nephritis were selected. They attended the clinic of medical city for outpatient from January 2012 to October 2013, and follow-up was done with them for more than six months. Among the 43 patients, 34 patients received cyclophosphamide for induction and mycophenolate was given to nine of them. Estimation of glomerular filtration rate (eGFR) and proteinuria at 6 months was done in these patients. They were also evaluated for response.

Results

The study results showed that 44% of patients responded partially or completely at 6 months and 64% of the patients responded at 1 year. Factors that correlate with the response at 6 months are hypertension, older age at diagnosis, activity, chronicity indices and the time frame of symptoms before the therapy. At 6 months, the predictors of response by logistic regression are chronicity index and hypertension. In current study, the patients with proliferative lupus presented with a lower proteinuria, lower eGFR, and higher chronicity scores, when compared to the Caucasian and African American patients. Hypertension, older age at diagnosis, chronicity indices, activity and the time frame of symptoms correlated with response. Short term outcomes were found to be similar to those explained in Caucasian patients.

KEYWORDS: *Lupus Nephritis, Outcomes, Cyclophosphamide & Mycophenolate.*

Original Article

Received: Oct 02, 2017; **Accepted:** Oct 21, 2017; **Published:** Nov 27, 2017; **Paper Id.:** IJMPSDEC20173

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem and auto immune disorder. It is an unpredictable disease, which is also episodic in nature. The serious complication of SLE is Lupus nephritis that is an inflammation of kidney. The kidney disease is influenced by mortality and morbidity, both directly and indirectly through the therapy that has lot of complications. The prevalence and incidence of SLE depends on the

patients chosen for studies and the diagnostic criteria for defining SLE. Males are outnumbered by females about one to ten. It has been observed that the males suffering from SLE have the same incidence of renal disease as that of females.

SLE can be diagnosed by the presence of certain laboratory and clinical features as defined by modified American Rheumatism Association (ARA) criteria in 1997. If four or more of the provided criteria is present, there would be 96% sensitivity and specificity for lupus diagnosis.

The histopathology of lupus is found to be pleomorphic in nature. The classification of the 2003 International Society of Nephrology (ISN)/Renal Pathology Society (RPS) of LN, which was formulated by the joint working group of RPS and ISN has been accepted by pathologists, nephrologists and rheumatologists. It has established to be more reproducible. More standardized definitions are also provided than the earlier WHO classification by it for exact clinical pathologic correlations. It has also been found to be more useful by some investigators to grade biopsies for chronicity (irreversible lesions) and activity features (potentially reversible lesions).

One of the serious complications of SLE is renal involvement. Classes III and IV proliferative lupus nephritis are found to have poor outcomes.

Focal proliferative diseased patients are found to have an extreme varied course. The patients with mild propagation with little percent of glomeruli respond fine to therapy, and over 5 years, lesser than 5% progress to renal failure.

Patients with necrotizing features, more proliferation and crescent formation have a prognosis similar to the patients with class IV diffuse proliferative disease. There are chances that the class III patients move into class IV over the period of time. The patients with diffuse proliferative disease are found to have the least positive prognosis in the older series. However, there has been marked improvement in the prognosis of this group, as in some series of patients that were treated with modern immunosuppressive agents, there has been renal survivals exceeding 90%.

The patients' survival has improved with the start of induction therapy with cyclophosphamide, with 5-year survival for class IV LN at 82%.

The delay in diagnosis and timely therapy, results in chronic changes that are difficult to reduce. Patients those who fail to achieve reduction are found to be at higher risk of flares of greater severity and worse renal survival. In the patients, those who achieve remission, there are chances of 95% survival, and 60% survival in those who do not; 94% of renal survival and 31% respectively. This study was conducted from a single center in Bhagdad (Medical city complex) to determine the epidemiological profile, clinical features, and short term outcomes in patients that suffer with lupus nephritis.

Patients and Method

For this study, a total of 43 patients belonging to III/IV lupus nephritis were selected. They attended the clinic of medical city for outpatients from January 2012 to October 2013, and follow-up was done with them for more than six months. Patients in all age groups were considered. However, those who are deemed to be in ESRD were excluded. Also, for whom six of therapy could not be provided due to infection or death is excluded.

Investigations like urinalysis, blood urea, complete blood count, serum creatinine and 24 hour urine protein excretion were performed in all the patients. Immunological investigations like anti-ds DNA, antinuclear antibody (ANA), and complements level were also conducted for all the patients.

The patients selected were subjected to percutaneous renal biopsies. Pathologists viewed the slides and they were processed for immune-staining technique and for light microscope. There would also be categorization of renal biopsies according to WHO/RPS/ISN classification and the chronicity and activity indices were observed.

It has been observed that the adequate biopsy specimen contained 10 glomeruli at least. The presence of renal function impairment and urinary abnormalities are indicated by the percutaneous renal biopsies in these patients, which guides the initial treatment.

Active LN was shown by RBC/WBC/ granular casts in the urine or RBC>5/hpf, proteinuria of more than 0.5 gm/day, and renal disease that is biopsy-proven.

The patients were given induction therapy with intravenous pulse methyl- prednisolone of 1000 mg once daily for three days. Among all the patients, 34 patients got induction with monthly intravenous pulse cyclophosphamide, 500-750 mg/m² body surface area. The dose is adjusted based on nadir leukocyte counts, which is to be kept above 3000/mm³. This is done on the 10th day after administration. Dosage was then adjusted to renal function, with a reduction of 25% for an eGFR of <15 ml/min. Oral prednisone was received by all the patients for six weeks at a rate of 0.5-1 mg /kg /day. As per the clinical improvement, this was gradually tapered by 10 mg/week to a maintenance dose of 5-7.5 mg/day. Among all the patients, 9 patients received induction with mycophenolatemofetil (MMF) daily with 500 mg four to six tablets along with prednisone.

All the patients were administered with angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor antagonists and hydroxyl-chloroquine. Increased oral prednisone or additional IV methylprednisolone pulses were used, for treating renal flares. Cyclophosphamide was given for Mesna.

Complete Response (CR) was the primary outcome measure. According to the EULAR consensus statement, this was defined as inactive urinary sediment, a decrease in proteinuria to ≤ 0.2 g per day and stable or normal renal function. A Partial Response (PR) was defined as inactive urinary sediment, proteinuria of ≤ 0.5 g per day, and stable or normal (if previously abnormal) GFR. The failure in treatment is defined as one of the following - a rise in creatinine of >0.6 mg/dl above the baseline, proteinuria of more than 3gm/day, estimated GFR dropping to below 15% of the baseline value, or discontinuation of treatment due to side effects.

The presence of renal relapses is considered if any of the following occurs: (1) reappearance of active sediment, (2) increase of proteinuria by 0.5 g/day to a value more than 1g/day in a patient before in PR or CR, (3) a decrease in estimated GFR by 30 ml/min. Some patients were defined with continuing disease activity, as they are found to have a proteinuria of >0.5 gm and <3 gm/day, and did not suit into either definitions of remission or failure.

Patients were requested to attend the OP department for first 6 months, once in every two weeks. Then, they were requested to make monthly visits for another 3 months, then 2-monthly till the study period's end. During each visit, SLEDAI scores, blood pressure, and existence of adverse events were noted. The laboratory tests like C3, 24-h protein excretion, anti-dsDNA at baseline were done at 6-monthly intervals. For the first 6 months, the fasting sugar, complete blood count, urea, and creatinine test were also carried out at monthly intervals for the first six months and then, during every clinical visit.

From the CKD-EPI equation (using three variables), estimated GFR (eGFR) was calculated, for patients with the age >16 years. For the patients below 16 years of age, Schwartz equation is used. Secondary end points contained any

partial or complete response, proteinuria at six months and one year, and eGFRs, renal relapses, adverse effects, and progression to ESRD, treatment failures, or death.

Statistical Analysis

With the help of statistical package for social sciences (SPSS) version 21, IBM, US, 2014, the details of all the 43 patients were entered and analyzed. Descriptive statistics were presented for continuous variables as standard deviation (SD) and as mean. Statistics were present for categorical variables as percentages (%) and frequencies (NO). To detect any differences, one-way ANOVA was performed in the laboratory (continuous) and clinical variables among the patients with complete, partial, or no responses for six months. To detect the differences in categorical variables in the same groups, Chi square test was performed. To find out the relationship between proteinuria, eGFR, and response at six months and laboratory and baseline clinical variables, Pearson's correlation test (bivariate) was performed. In addition to P-value, Correlation coefficient (R) was calculated. The value of R ranging between 0 and 1 indicated the correlation strength. When the strongest correlation is significant, it is indicated by the highest R value. The direction of the correlation is indicated by the sign of R and the negative signed R value (-R) shows negative inverse correlation. No signed R showed a positive (direct) correlation. To detect predictors of outcome, stepwise multiple logistic regression analysis was performed at 6 months in terms of eGFR and proteinuria at 6 months. To determine predictors of partial, complete and no remission, logistic regression analysis was performed. The tests were also done to determine odds ratio, the beta, R, and P-values. The higher prediction value of a variable is indicated by the variable with the higher odds ratio/ beta value. Level of P-value, <0.05 is considered to be significant.

RESULTS

In this prospective study, 43 patients were enrolled. Their baselines and clinical studies are present in table 1.

The age group selected as 25 ± 9.7 years. In the studied group, females were dominant comprising 89.5% (39 members) of females and 10.5% (4 persons) of males. At the time of diagnosis, the mean age was (22 ± 10) years. There were reports of arthritis in 29 patients (67.4%), fever at presentation in 27 (62.8%), oral ulcers in 21 (48.8%), rash in 27 (62.8%), hypertension at onset in 24 (55.8%), serositis in 9 (20.9%), photosensitivity in 17 (39.5%), hair loss in 20 patients (46.5%) and CNS manifestation in 5 (11.6%). The mean period of symptoms before the therapy was 11.9 ± 14.1 months.

Table 1: Baseline clinical characteristic of 43 Patients

Characteristics	No. (%)
Age (years)	25±9.7
Gender (M/F)	4 (10.5%)/39 (89.5%)
Age at diagnosis (years)	22±10
Arthritis	29 (67.4%)
Rash (malar or peripheral)	27 (62.8%)
Fever at presentation	27 (62.8%)
Hypertension at onset	24 (55.8%)
Oral ulcers	21 (48.8%)
Hair loss	20 (46.5%)
Photosensitivity	17 (39.5%)
Serositis (Pleuritis of pericarditis)	9 (20.9%)
CNS manifestations	5 (11.6%)

Duration of symptom prior to therapy (months)	11.9±1 4. 1
---	-------------

Table 2 shows the summarized laboratory findings of the group that was studied. It has been observed that 4 patients (9.3%) had thrombocytopenia (platelets count $< 150 \times 10^3 / \text{mm}^3$), 33 patients (76.7%) had positive anti dsDNA ($> 15 \text{ IU/ml}$), 2 patients (4.7%) had leucopenia (WBCs count $< 4000 \text{ cells/mm}^3$), and 18 patients (41.9%) had nephrotic range proteinuria. In other words, the mean hemoglobin was $9.27 \pm 2.3 (\text{mg/dl})$, the mean serum creatinine was $1.62 \pm 1.38 (\text{mg/dl})$, the mean SLEDAI score was 17.8 ± 4.5 , the mean serum albumin was $3.09 \pm 0.77 (\text{g/dl})$, the mean activity index was 7.3 ± 3.7 , the mean urine protein excretion was $2.60 \pm 1.66 (\text{g/24h})$, the mean eGFR was $67.1 \pm 38.7 (\text{ml/min/1.73})$ and the chronicity index was 1.2 ± 1.9 .

Biopsy class IV has been observed in 35 patients (81.4%), biopsy class III was in 5 patients (11.6%), and biopsy class IV+V was found in 3 patients (7%). 14 patients (32.6%) have been found to be with eGFR at presentation of $> 90 \text{ ml/min}$, eGFR at presentation of 30-60 ml/min in 5 patients (11.6%), eGFR at presentation of 60-90 ml/min in 9 patients (20.9%), and eGFR at presentation of $< 15 \text{ ml/min}$ was found in 4 patients (9.3%).

By 6 months, 10/43 (23.3%) patients are found to be in complete response, 9/43 (20.9%) patients were found to be in partial response, and 6/43 (13.9%) patients were found to be in treatment failure. Remaining 41.9% of patients are found to have continued disease activity, but have not yet reached the end point. Within six months of the onset of the induction period, three patients went into ESRD. It has been found that the average time to achieve partial remission was $3.9 (\pm 2.2)$ months and to achieve complete remission was $4.5 (\pm 1.9)$ months.

Table 2: Baseline laboratory values in patients (No. of patients =43)

Characteristics		Values
Leucopenia		2 (4.7%)
Thrombocytopenia		4 (9.3%)
Anti dsDNA positive ($> 15 \text{ IU/ml}$)		33 (76.7%)
Nephrotic range proteinuria		18 (41.9%)
SLEDAI score		17.8 ± 4.5
Hemoglobin (g/dl)		9.27 ± 2.3
Serum Albumin (g/dl)		3.09 ± 0.77
C3 (mg/dl)*		76.8 ± 34.2
Urine protein excretion (g/24 h)		2.60 ± 1.66
Serum creatinine (mg/dl)		1.62 ± 1.38
eGFR (ml/min)		67.1 ± 38.7
Activity index		7.3 ± 3.7
Chronicity index		1.2 ± 1.9
Biopsy class III		5 (11.6%)
Biopsy class IV		35 (81.4%)
Biopsy class IV+V		3 (7.0%)
eGFR at presentation	$> 90 \text{ ml/min}$	14 (32.6%)
	60-90 ml/min	9 (20.9%)
	30-60 ml/min	11 (26%)
	15-30 ml/min	5 (11.6%)
	$< 15 \text{ ml/min}$	4 (9.3%)

*Normal C3 level between 90-180 mg/dl

Comparison of Mean Values of Patients Parameters According to Response

To compare the mean values of parameters of different patients along with the response to treatment, the categories like complete/partial/no response, analysis of variance (ANOVA) tests were conducted. By this test, it was found that there are no significant differences in mean age, proteinuria, hemoglobin, eGFR and activity index among the patients with complete or partial response (in all these comparison $P > 0.05$) and in those with no response. It was found that, in the patients with complete response (0.25 ± 0.64), Chronicity Index was considerably lower as compared to those with no or partial response - (1.62 ± 2.11) and (1.0 ± 1.71) respectively, ($P = 0.017$). The timeframe of the symptoms before the therapy were considerably lower in patients with complete response (6.7 ± 10.0) than those with no response (16.5 ± 15.7) and those with partial response (15.5 ± 11), ($P = 0.029$). All these observations are shown in the table 3.

Table 3: Results of ANOVA Test between important Baseline Clinical and Laboratory Variables Distributed by Response Categories

Variable	No Response	Partial Response	Complete Response	P-Value
Age (years)	26.2±11.0	25.6±8.4	21.7±9.8	0.215
Hb (g/dl)	9.7±2.1	8.2±2.5	9.2±2.2	0.053
Proteinuria (g/24 hr)	2.78±1.78	2.83 ± 1.34	1.96±1.49	0.142
eGFR (ml/min)	63±38	64±39	81 ±41	0.208
Activity index	7.9±3.5	7.1±4.9	6.0±2.6	0.145
Chronicity Index	1.62±2.11	1.0±1.71	0.25±0.64	0.017*
Duration of symptoms prior to the therapy (months)	16.5±15.7	15.5±11.0	6.7± 10.0	0.029*

To assess the correlation between baseline patients' variables and outcome, Pearson's correlation test (correlational statistical test) was used. A significant correlation was found between eGFR at 6 months and age at hypertension, baseline renal function, proteinuria, diagnosis, and percentage of glomeruli in the biopsy sample, that contains the activity, crescents, and chronicity indices. At 6 months, the response correlation with age at activity, diagnosis, chronicity indices, hypertension, and duration of symptoms. There was no correlation of mycophenolate or cyclophosphamide related treatment with any of the outcome variables.

Table 4: Pearson's and Point Bi-Serial Correlation between Outcomes and Baseline Variables

Baseline Variables	R Values	R Values	R Values
	eGFR at 6months	Proteinuria	Response
Age at diagnosis	-0.563*	0.121 ^{NS}	-0.119 ^{NS}
Hypertension	-0.270*	0.250*	-0.274*
SLEDAI	-0.260*	0.972 ^{NS}	0.998 ^{NS}
Proteinuria	-0.278*	0.362 ^{NS}	-0.183 ^{NS}
Nephrotic syndrome	-0.217*	0.143 ^{NS}	-0.207 ^{NS}
eGFR (baseline)	0.575*	-0.117 ^{NS}	0.176 ^{NS}
Crescents among Glomeruli	-0.287*	-0.133 ^{NS}	-0.133 ^{NS}
Activity index	-0.467*	0.116 ^{NS}	-0.213*
Chronicity index	-0.571*	0.215*	-0.305*
Duration of symptoms	-0.109 ^{NS}	0.170 ^{NS}	-0.264*
Therapy	0.058 ^{NS}	-0.081 ^{NS}	0.027 ^{NS}

Multiple Logistic Regression Tests

To estimate the correlations between the outcome and the baseline variable, multiple logistic regression (a statistical test), of stepwise model, was carried out. This is also to detect the eGFR predictors at 6 months. As shown by the statistical test, eGFR at baseline was the most predictor of eGFR at 6 months, [R= 0.56, odds ratio = 6.05, P=0.0011], followed by chronicity index [R= 0.65, odds ratio = 4.95, P=0.002]. The least predictor was the age at diagnosis [R= 0.48, odds ratio =1.47, P=0.003]. As shown in table 4, despite the correlation between each of activity index and outcome and duration of symptoms at bivariate (Pearson) statistical correlation tests, the variables on multiple logistic regression tests, showed no significant correlation as they are not the forecaster for the outcome. This insignificance indicated that the significant correlation in Pearson's test might feature the effect of other variables which vanished when controlled for in the multiple logistic regressions as a part of the test design. This is shown in table 5.

Table 5: Results of Multiple Logistic Regression Test (Stepwise) for Prediction of eGFR at 6 Month

	B	R	Odds Ratio	P
Age at diagnosis	0.39	0.48	1.47	0.003
Hypertension	0.16	0.14	1.10	0.36
SLEDAI	0.28	0.27	1.32	0.29
Proteinuria	-0.12	0.15	1.12	0.67
Nephrotic syndrome	- 0.17	0.20	1.18	0.46
eGFR (baseline)	1.8	0.56	6.05	0.0011
Percentage of crescents among glomeruli	-0.22	0.14	1.24	0.61
Activity index	-0.27	0.22	1.31	0.87
Chronicity index	- 1.6	0.65	4.95	0.002
Duration of symptoms	-0.42	0.25	1.52	0.17
Therapy	0.21	0.10	1.20	0.95

The absence of chronicity index (R= 0.30, odds ratio= 1.39, P=0.043) and hypertension (R= 0.33, odds ratio = 2.7, P=0.044) were found to be the predictors of response (partial or complete) at 6 months as revealed by logistic regression analysis as shown in table 6.

Table 6: Results of Multiple Logistic Regression Test (Stepwise) for Prediction of any Response (Partial or Complete)

	B	R	Odds Ratio	P
Absence of Hypertension	0.994	0.33	2.70	0.044
Chronicity index	-0.330	0.30	1.39	0.043

In the first 6 months of follow-up, there were no renal flares. Renal flares occurred in 2/21 patients (9.5%) in the first year among the patients those who were followed-up beyond 6 months. Both the patients were found to be characterized by increased proteinuria with no active sediment. The time to flare was observed to be nine months in one patient and seven months in another patient. The responded patients went into remission by the first year end. One of the 13 patients comprising 7.7% was found to have flares in the 2nd year, characterized by the presence of proteinuria, at 13 and 16 months respectively;

DISCUSSIONS

Considerable improvement in the lupus nephritis patients' survival has been observed, which has contributed to earlier referral to nephrologists, improved awareness, effectiveness of newer induction regimens, and an overall enhancement in medical care. Different studies and trials comparing the LN outcomes have been confounded by the variations in histology (classes III, IV and V lesions), different criteria for remission, different treatment regimens, relapse, and flare. The criteria of the American College of Rheumatology (ACR) for remission are a composite of urinary protein to creatinine ratio ≤ 0.2 mg/mg, estimated GFR of >90 ml/min, and inactive urinary sediment. It is very difficult to achieve complete remission (normal renal function), especially in patients with higher chronicity indices. Normal or stable GFR is accepted for both partial response and complete response, according to the EULAR response criteria. National Institute of Health (NIH) has defined the patients with refractory disease as those who show no response to the treatment, who have determined active urinary casts or decline in serum creatinine level, and whose proteinuria level does not decrease to less than half of pretreatment value or to <3 g per day. The patients in the current study are found to have higher creatinine level compared to the Africa American and Caucasian patients, but a lower degree of proteinuria at baseline. At onset and lower activity, they also had a young age, but higher chronicity indices on renal biopsy

In the patients, the rates of response were 23% and 21% for PR and CR at 6 months respectively. 53% patients got the primary efficacy end point in the cyclophosphamide arm of the ALMS study at 6 months. This has been well-defined as a decrease in urine protein/creatinine ratio (P/Cr), which was estimated using a 24-h urine collection, to <3 in patients with baseline nephrotic range P/Cr (>3), or by $>50\%$ in patients with sub-nephrotic baseline P/ Cr (<3). More number of patients reached partial or complete response on follow-up (64%) at the 1st year end. When compared with the Chinese patients those who were followed-up for long-term follow-up revealed at least partial or complete response rate of 82% and 55%. In European Caucasian population, the response was 62 and 88% in one study. For remission, the median time is usually longer than 6 months.

On an average, a delay of 12 months has been observed in the patients from the start of the disease to the beginning of therapy. This delay was found to be more in patients with no response versus those who have attained complete response. This is the refractory disease's cause.

Proteinuria decrease acts as the marker for renal outcomes. The observation shows that the response of the patients was in association with non-significant fashion towards reduced degrees of proteinuria. Early response to therapy by 6 months was demonstrated by multivariate analysis in the long-term outcomes of the Euro-Lupus cohort. This is stated as creatinine decline and proteinuria decrease at 6 months, to less than 1 gm/day, which predicted the long-term outcomes.

One of the poor prognostic markers is a younger age at diagnosis. The patients' age at diagnosis ranged from 9 to 48 years in our study, among which five patients were lesser than 12 years during diagnosis. The diagnosed age as well as the percentage was negatively correlated with eGFR and response at 6 months. Longer latency for treatment in older age patients could have been the reason for this. Hypertension, presence of crescents, renal impairment at baseline, and a higher chronicity index at baseline are the other markers of poor prognosis, which were corroborated in the research.

There was variation in the reported rates of relapse from 25% to 46% at 5 years and 10 years, respectively. To provide the relevant relapse rates, the follow-up timeframe was too short, but there was a relapse for two patients in the 1st and 2nd years. After the first 6 months, 14% of the patients experienced treatment failure, which was similar to the

treatment failure rate (20% in the high-dose arm; 16% in the low-dose cyclophosphamide arm) in the Euro Lupus trial.

A research conducted in India shows that the average time for remission was 15 months in a cohort of Class IV predominant lupus patients and rates of remission were 82.05%. Predicted remission is used by ACEi/ARB, early diagnosis, and a higher creatinine at presentation in this study. The risk factors for poor outcome in another study that concentrated on long-term survival in LN are hematuria, creatinine, and hypertension, occurrence of a major infection and lack of remission.

Reports from another study showed that there are better outcomes (84.6% were in complete or partial remission) from pediatric lupus at one year. A research from Eastern India showed in the pediatric population that the overall male to female ratio was 1:3.8. It was also observed that the manifestations in renal was present in 54% of the patients. The predominant histological presentation in kids was diffuse proliferative glomerulonephritis (WHO class IV) that was found to be common in boys rather than girls. When compared to adult women, the adult men had severe renal impairment (60% vs. 37.5%), with higher blood urea (63.25 vs. 48 mg/dL) and higher levels of mean serum creatinine (2.67 vs. 1.62 mg/dl).

A group of patients with proliferative lupus nephritis was evaluated in the current study. Their response to the therapy was assessed along with its predictors in short term. The outcomes were found to be negatively correlated with the age at baseline. At 6 months, the major variances to predict the eGFR were found to be the chronicity index, eGFR at baseline and age at diagnosis. Few other factors for poor prognosis were proteinuria, hypertension, and percentage of glomeruli in the biopsy specimen containing crescents, eGFR at baseline, and activity and chronicity indices.

To conclude, the study showed that there has been a significant improvement in patients' survival, those who were suffering with LN. This has been associated to increased awareness, earlier consultations with nephrologists, effectiveness of fresher induction schedules, and a complete progress in medical care. At 6 months, half of the patients had complete or partial response and about 2/3rd of the patients at one year. At six months, the factors correlating with response are hypertension, older age at diagnosis, chronicity indices, activity, and duration of symptoms prior to therapy. The predictors of response by logistic regression were hypertension and chronicity index. When Caucasian patients are compared with African American patients, patients with proliferative LN showed lower eGFR, higher chronicity scores and lower proteinuria. There were no correlations by the treatment provided by mycophenolate or cyclophosphamide with the outcomes variables. As those explained in Caucasian patients, the short term outcomes were similar.

Specialized outpatient clinics are recommended due to the increasing number of SLE patients. It is also recommended to have multidisciplinary teams with early referral of Systemic Lupus Erythematosus patients for any suspension of renal involvement. There should also be the availability of facilities that could not be afforded by the patients at high cost. Providing biologic agents like anti-CD20 (rituximab), immune modulating agents like IV gamma globulin and fully humanized anti-CD20 (ocrelizumab) for refractory cases are also highly recommended.

REFERENCES

1. Bomback AS, Appel GB. Update on the treatment of lupus nephritis. *J Am Soc Nephrol.* 2010;21:2028-2033.
2. Appel GB, D'Agati VD: Lupus nephritis—pathology and pathogenesis. In Wallace DJ, Hahn BH, eds. *Dubois' Lupus Erythematosus*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:1094-1112.
3. *Erythematosus*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:1094-1112.

4. Appel GB, Jayne D. Lupus nephritis. In: Johnson R, Floege J, Feehally J, eds. *Comprehensive Clinical Nephrology*. St. Louis: Elsevier; 2010.
5. Appel GB, D'Agati V. Renal involvement in systemic lupus erythematosus. In: Massary S, Glassock R, eds. *Text of Kidney Disease*. St. Louis: Williams & Wilkins; 2000:787-797.
6. Tutuncu ZN, Kalunian KC: The definition and classification of SLE. In Wallace DJ, Hahn BH, eds. *Dubois' Lupus Erythematosus*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:16-21.
7. Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med*. 2008;358:929-939.
8. Rus V, Maury EE, Hochberg MC: The epidemiology of SLE. In Wallace DJ, Hahn BH, eds. *Dubois' Lupus Erythematosus*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:34-43.
9. Waldman M, Appel GB. Update on the treatment of lupus nephritis. *Kidney Int*. 2006;70:1403-1412.
10. D'Agati VD. Renal disease in systemic lupus erythematosus, mixed connective tissue disease, Sjogren's syndrome, and rheumatoid arthritis. In: Jennette CJ, Olson L, Schwartz MM, et al., eds. *Pathology of the Kidney*. 5th ed. Philadelphia: Lippincott-Raven; 1998.
11. Weening JJ, D'Agati VD, Appel GB, et al. The classification of glomerulonephritis systemic lupus nephritis revisited. *Kidney Int*. 2004;65:521-530.
12. Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. *Kidney Int*. 2007;71:491-495.
13. Markowitz GS, D'Agati VD. Classification of lupus nephritis. *Curr Opin Nephrol Hypertens*. 2009;18:220-225.
14. Austin HA, Boumpas DT, Vaughan EM, et al. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int*. 1994;43:544-550.
15. Pollak VE, Pirani CL, Schwartz FD. The natural history of the renal manifestations of systemic lupus erythematosus. *J Lab Clin Med* 1964;63:537-50.
16. Appel GB, Cohen DJ, Pirani CL, et al. Long term follow-up of lupus nephritis: a study based on the WHO classification. *Am J Med*. 1987;83:877.
17. Schwartz MM, Lan S-P, Bernstein J, et al. Role of pathology indices in the management of severe lupus glomerulonephritis. *Kidney Int*. 1992;42: 743-748.
18. Balow JE, Boumpas DT, Fessler BJ, et al. Management of lupus nephritis. *Kidney Int*. 1996;49(suppl):S88-S92.
19. Behara VY, Whittier WL, Korbet SM, et al. Pathogenetic features of severe segmental lupus nephritis. *Nephrol Dial Transplant*. 2010;25:153-159.
20. Austin HA, Boumpas DT, Vaughan EM, et al. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int*. 1994;43:544-550.
21. Valeri A, Rhadhakrishnan J, D'Agati V, et al. IV pulse Cyclophosphamide treatment of severe lupus nephritis. *Clin Nephrol*. 1994;42:71-78.
22. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum*. 1991;34:945-950.
23. Cameron JS. Lupus nephritis. *J Am Soc Nephrol* 1999; 10:413-24.

24. Ioannidis JP, Boki KA, Katsorida ME, Drosos AA, Skopouli FN, Boletis JN, et al. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. *KidneyInt* 2000;57:258-64.
25. Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus nephritis collaborative study group. *Am J Kidney Dis* 2000; 35:904-14.
26. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;15:241-50.
27. Gordon C, Jayne D, Pusey C, Adu D, Amoura Z, Aringer M, et al. European consensus statement on the terminology used in the management of lupus glomerulonephritis. *Lupus* 2009;18:257-63.
28. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong Guangzhou Nephrology Study Group. *N Engl J Med* 2000;343:156-62.
29. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 2009;4:1832-43.
30. Liang MH, Schur PH, Fortin P, et al. The American college of rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. *Arthritis Rheum* 2006;54:421-32.
31. Boumpas DT, Balow JE. Outcome criteria for lupus nephritis trials: A critical overview. *Lupus* 1998;7:622-9.
32. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: The euro-lupus nephritis trial, a randomized trial of low- dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46:2121-31.
33. Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, et al. Influence of race/ethnicity on response to lupus nephritis treatment: The ALMS study. *Rheumatology (Oxford)* 2010;49:128-40.
34. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;20:1103-12.
35. Ginzler EM, Wofsy D, Isenberg D, Gordon C, Lisk L, Dooley MA, et al. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: Findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. *Arthritis Rheum* 2010;62:211-21.
36. Mok CC, Ying KY, Tang S, Leung CY, Lee KW, Ng WL, et al. Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthritis Rheum* 2004;50:2559-68.
37. Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P, Ponticelli C. The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant* 2007;22:2531-9.
38. Gourley MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 1996;125:549-57.
39. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term follow up of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum* 2004;50:3934-40.
40. Esdaile JM, Levinton C, Federgreen W, Hayslett JP, Kashgarian M. Clinical and renal biopsy predictors of long-term outcome in lupus nephritis: A study of 87 patients and review of the literature. *Q J Med* 1989;72:779-833.
41. Lupus nephritis: prognostic factors and probability of maintaining life-supporting renal function 10 years after the diagnosis.

- Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL). Am J Kidney Dis.* 1992;1 9:473-9.
42. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: Contributions of clinical and histologic data. *Kidney Int* 1994;45:544-50.
 43. Lim CS, Chin HJ, Jung YC, Kim YS, Ahn C, Han JS, et al. Prognostic factors of diffuse proliferative lupus nephritis. *Clin Nephrol* 1999; 52:139-47.
 44. Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. *Kidney Int* 1996;50:2047-53.
 45. Ciruelo E, de la Cruz J, López I, Gómez-Reino JJ. Cumulative rate of relapse of lupus nephritis after successful treatment with cyclophosphamide. *Arthritis Rheum* 1996;39:2028-34.
 46. Annavarajula SK, Murty KV, Prayaga A, Das U, Desai M, Narain CA. The outcome of proliferative lupus nephritis with pulse cyclophosphamide therapy. *Indian J Nephrol* 2011 ;21 :160-5.
 47. Dhir V, Aggarwal A, Lawrence A, Agarwal V, Misra R. Long-term outcome of lupus nephritis in Asian Indians. *Arthritis Care Res (Hoboken)* 2012;64:713-20.
 48. Hari P, Bagga A, Mahajan P, Dinda A. Outcome of lupus nephritis in Indian children. *Lupus* 2009;18:348-54.
 49. Mondal R, Nandi M, Ganguli S, Ghosh A, Hazra A. Childhood lupus: Experience from Eastern India. *Indian J Pediatr* 2010;77:889-91.
 50. Gupta KL. Lupus nephritis in children. *Indian J Pediatr* 1999; 66:215-23.
 51. Soni SS, Gowrishankar S, Adikay GK, Raman A. Sex-based differences in lupus nephritis: A study of 235 Indian patients. *JNephrol* 2008;21 :570-5.