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Research Article

Diagnose

Efficacy of standard treatment protocol in recently diagnosed Lupus Nephritis at our tertiary care teaching hospital

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Introduction: Lupus Nephritis occurred in approximately 50% of Systemic Lupus Erythematosus patients at some point during their illness and is associated with a poor prognosis. **Material and Method**: A prospective observational study of 50 newly diagnosed LN cases was conducted to investigate the response of standard treatment protocol (Cyclophosphamide -NIH protocol and Mycophenolate Mofetil-MMF). **Results:** Of the 50 newly diagnosed cases of LN, 94 % (n=47) were females, and 6 % (n=3) were males, with class IV LN accounting for the majority of patients 69.39 % (n=34). At six months, 36.7 % (n=11) of patients in the cyclophosphamide (CYP) group had a complete response. Only 27.3 % of patients in the MMF group had a complete response; however, this difference was not statistically significant. At the end of one year, only 56.7 % of the CYP group and 81.8 % of the MMF group had a complete response; however, this difference was not statistically significant (p=0.282). Although the initial response with CYP was better and later in the MMF group, these differences were not significant statistically. Tuberculosis or its reactivation was the most common complication during treatment, either with MMF or CYP. One patient died due to latent tuberculosis reactivation, another as a result of severe disease activity at presentation (proteinuria was 20 gm/24 hours in that patient), and the third as a result of pneumonia with septicemia. **Conclusion:** Treatment with either CYP or MMF is equally effective, but underlying infection, particularly tuberculosis, should be ruled out before initiating therapy.

Keywords: Lupus Nephritis, Systemic lupus erythematosus, Cyclophosphamide, Mycophenolate mofetil

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Introduction

Renal glomeruli are the most involved structure, presenting as lupus nephritis (LN) in Systemic Lupus Erythematosus (SLE). Immune complex formation and deposition – circulating or in situ – in the mesangium, subepithelial, or subendothelial layers initiate the pathogenic events that result in histopathological changes in the glomeruli. The renal disease occurs in up to 25-60% of SLE patients, most frequently within five years of disease onset.

It is regarded as one of the most powerful predictors of an unfavourable outcome, which eventually affects about half of all patients at some point during their illness.[1,2]. LN defined as per SLEDAI definition [3,4]. if any of the four following criteria are met;1. Urinary casts (Heme-granular or red blood cells casts.) 2. Haematuria (> 5 red blood cells/high power field, excluding stone, infection, and other causes). 3. Proteinuria (>0.5 g/24h, regarding new-onset or recent increase of >0.5g/24h). 4.

Pyuria (> 5 white blood cells/high power field, excluding infection). LN classified into six classes by the International Society of Nephrology and Renal Pathology Society (ISN/RPS) to provide a more concise description of various lesions and classes of LN.[5]. We conducted a Prospective observational study to investigate the response of standard treatment protocol (CYP -NIH protocol and MMF)

Aims And Objectives

To study the response of LN to standard treatment at the end of the study

- response in clinical and laboratory parameter over one year follow up

- assess the frequency of total and partial remission at six months and 12 months

Material and Methods

Study design: An observational and prospective study from Aug 2010 to Aug 2012. The study was approved by the Institutional Ethics Committee.

Setting - From August 2010 to August 2012, fifty newly diagnosed LN cases were included in the study. All of these LN patients met the ACR's 1997 revised SLE classification criteria.[6]. For one year, all patients were followed up at least three times a month, and more frequently if necessary.

Inclusion criteria:

1) Patients diagnosed as SLE based on the American College of Rheumatology (ACR) criteria.

2) Patients (or their guardians) should give informed consent for the investigations.

3) Age >12 yrs.

Exclusion criteria: Patients with 1) Already diagnosed with Lupus Nephritis 2) Overlapping feature of other Glomerulonephritis 3) Pregnancy 4) HIV infection

Consent: All patients or their relatives/guardians provided written informed consent for blood sampling and renal biopsy. Study procedure: In this study, 50 consecutive subjects who met the inclusion criteria were recruited over a year and then followed up for another year.

History: During the follow-up, the onset, duration, and progression of all symptoms and clinical manifestations were recorded. Clinical examination: At each visit, general and systemic examinations were performed. Investigation and follow up: Routine investigations: Complete hemogram, Erythrocyte sedimentation rate(ESR), Renal function tests, Liver function tests, serum uric acid, Total protein, albumin, Fasting, and postprandial blood sugar, Lipid profile, HIV, CPK(Creatine phosphokinase) whenever indicated, Thyroid function test, Urine routine, and microscopic examination, 24-hour urinary protein, Chest radiograph- posteroanterior view, ECG,

Special Investigations: ANA by immunofluore-scence Anti ds-DNA by indirect immunofluorescence C3 and C4 complement levels (with BNProSpec KIT by nephelometric assay with normal range of C3 – 90- 180 mg/dl and C4- 15- 45 mg/dl) ACLA (anticardiolipin antibody) IgG and IgM ANA blot if necessary ANCA (Antineutrophil cytoplasmic antibody) Direct and indirect Coomb"s test if required. USG (Ultrasonography) guided renal biopsy – All newly diagnosed cases of lupus nephritis are subjected to USG guided renal biopsy and are classified into six groups based on the ISN/RPS 2003 classification of LN. Histological criteria were used to determine activity (maximum score, 24 points) and chronicity indices (maximum score, 12 points). Other tests, such as 2D ECHO, USG abdomen and pelvis, computed tomography (CT), magnetic resonance imaging (MRI), and cerebrospinal fluid examination, were performed as needed.

Clinical evaluations and laboratory tests were performed on all patients at the start and three-month intervals, or more frequently if necessary. In addition, they were evaluated and managed for any complaints or complications that arose between these visits. All patients were followed from the time they were diagnosed with lupus nephritis until one year later.

Management: The patients were investigated and treated according to the standard LN treatment regimen. There were no experimental treatments, and the patient did not face any potential financial hardship due to this research. All patients received treatment as per standard protocol. All patients received Tab Prednisolone, Tab Aspirin, Tab. Hydroxychloroquine, statins, Vitamin D, Calcium supplements, ACE inhibitors, or blockers. Either Pulse Cyclophosphamide (CYP) therapy (as per NIH protocol) or Tab MMF (as per ALMS trial) was used for induction (for class III, IV, and V) after counselling about the advantage and disadvantages of each of these.[7,8]. Analysis: All data were entered into an Excel spreadsheet, and a descriptive analysis of the demographic and clinical profiles was performed using Mean, Range, and Cumulative Frequency as a percentage. The repeated test ANOVA was used to compare groups, and a p-value of 0.05 was considered statistically significant.

Results

Of the 50 newly diagnosed cases of LN, 94% (n=47) were females, and 6% (n=3) were males with a female to male sex ratio was 15.67 :1. The maximum number of patients were in between the 20-29 age groups. Out of 50 newly diagnosed cases of LN, most patients had class IV LN 69.39% (n=34) followed by Class II LN 14.29%(n=7), Class III and V LN 6.12 % each(n=3). Class VI and class I LN each 2.04 %(n=1), renal biopsy was not performed in one female patient because was expired soon after admission because of severe disease activity.

All 50 patients were ANA positive, out of which the most common pattern being homogeneous (60%) followed by Speckled (26%), Nucleolar (6 %), Cytoplasmic (4%), and Centromere (4 %) All patients received treatment as per standard protocol as mentioned above. Out of 50 patients enrolled,64%(n=32) were on Cyclophosphamide pulse regimen (NIH Regimen), 22% (N=11) were on MMF, 12%(n=6) were only on Tab Prednisolone (Class I and II LN), and one patient was on maintenance hemodialysis as diagnosed to have ESRD. The response to induction therapy either with Cyclophosphamide or MMF was assessed statistically in terms of complete remission, partial remission, and no response. Complete remission defined as urinary protein <500 mg/day with normal urinary RBC, normal serum albumin 3.5-5.5 gm/dl, and normal serum Creatinine.

Partial remission defined as stabilization or improvement of serum creatinine, RBC in urine < 5 cells/field, and persistent 24-hour reduction (if nephrotic, reduction more than or equal to 50 % but with a value lower than 3 gm/24 hours; if non-nephrotic, reduction more than or equal to 50 %; but with a value greater than 500 mg/24 hours). At six months of treatment, complete response was seen in 36.7%(n=11) in the cyclophosphamide group and only in 27.3% of patients in the MMF group, but this difference was not statistically significant. (P=0.614). At the end of one year, the complete response was seen in only 56.7 % in the cyclophosphamide group and 81.8 % in the MMF group; however, this difference was also not statistically significant(p=0.282) Though initial response was better with cyclophosphamide and later in MMF group, these were not statistically. significant. In the Cyclophosphamide group, out of 32,2 patients died before six months, so excluded from the analysis of response to treatment.

Table 1-Partial and Complete response to CYP and MMF at 6 months and 12 months

		CYP		MMF	
		Number of Patients	%	Number of Patients	%
At 6 months	Complete Remission	11	36.7 %	3	27.3 %
	Partial Remission	5	16.7 %	1	9.1 %
	No Response	14	46.7 %	7	63.6 %
	Total	30	100 %	11	100 %
At 12 months	Complete Remission	17	56.7 %	9	81.8 %
	Partial Remission	3	10 %	0	0 %
	No Response	10	33.3 %	2	18.2 %
	Total	30	100 %	11	100 %

The mean of 24 hours urinary protein at the enrollment of study was 2607.61 gm/24 hours with a maximum being 20000 gm/24 hours and minimum being 435 gm/24 hours and at the end of study mean was 492.25 gm/24 hours with a maximum of 2428 gm/24 hours and minimum being 97 gm/24 hours. The nephrotic range proteinuria was present in 20%(n=10) of patients, 70 % of which belonged to class IV LN (n=7), one patient had class V LN, one had VI LN, one died because of severe disease activity which had proteinuria 20 gm/24 hrs.

After excluding three which were expired during follow-up, there was a significant decrease in 24 hours urinary protein after treatment ($p < 0.001$). The repeated measure ANOVA was used for analysis. The C3 and C4 significantly increase the following treatment after the end of one year from a mean of 48.91 and 12.856 respectively to a mean of 130.13 and 36.45. (p-value 0.001 by using repeated ANOVA measure test.

All 50 patients were ANA positive with the different patterns as mentioned above, out of which 54% (n=27 were ds DNA positive) after the end of 1-year ds DNA positivity decreased to 14.89%(n=7) with treatment which was statistically significant. Out of 50 patient, 24% patients(n=12) developed complication during one year period, which was as follows

Table 2- Complication occurred during follow-up of LN patients over one year.

Complication	Number of patients
Pulmonary tuberculosis	2
Abdominal Koch's	1
Reactivation of tuberculosis	2
TB Lymphadenitis	1
Pancreatitis	2
Avascular Necrosis of the hip joint	1
Chickenpox infection	1
HZV infection	1
Thigh abscess	1
Total	12

At the end of one year: Living: 94%(n=47) Death: 6% (n=3) All death occurs within six months of diagnosis of LN. Out of 3 patients who expired, one died because of reactivation of latent TB, one had died because of severe disease activity at presentation, proteinuria was 20 gm/24 hours in that patient, and the remaining one died because of pneumonia with septicemia.

Discussion

In our study, a total of 50 newly diagnosed cases of LN patients based on ACR criteria were included. These were followed up prospectively quarterly for 1 year, more frequently if necessary. In our study, 94 % (n=47) of newly diagnosed LN cases were female, while 6 % (n=3) were male. The female to male ratio was 15.67:1. The average age at onset of LN was 26.18 ± 8.39 years. The majority of patients (54%) (n=27) were between the ages of 20 and 29, with only 8% (n=4) over the age of 40. The M: F ratio indicated a female predominance, but different ratios in different study groups could be due to differences in geographic area, genetic and environmental factors. The demographic profile at the time of LN diagnosis was comparable to other studies.[1,7].

The most common histological class was class IV (69.39%), similar to the other study, including those in India.[1,8,9]. Renal biopsy was not done in one patient as she expired soon after diagnosis of SLE because of severe disease activity. The mean of 24 Hours urinary protein at the start of the study was 2607.61 gm/24 hours, which reduced to 492.25 gm/24 hours at the end. Proteinuria in the nephrotic range was present in 20% (n=10) of patients, 70% (n=7) belonged to class IV LN, one patient had class V LN, one had VI LN, and one died due to severe disease activity with proteinuria of 20 gm/24 hrs. In the study by C Chrysochou et al. [10], 33 % had nephrotic range proteinuria, with 27 % having class IV LN, 64 % having class V LN, and % having class III LN.

According to studies, Indians have a higher percentage of nephrotic range proteinuria. Dhir et al [1]. found that 34.4 % in their study (north India) had nephrotic range proteinuria. In Raphael V's (Northeast India) study, 66.6 % had nephrotic range proteinuria. Both of the above Indian studies were retrospective. In our study, the percentage of nephrotic range proteinuria was only 20 % which could be because our study was prospective, which helps to detect proteinuria earlier and early initiation of appropriate treatments. We analyzed the treatment response in class III, IV, V LN who were either on cyclophosphamide or MMF for induction at six months and 12 months. (one patient with class II also included as was on cyclophosphamide for concomitant ILD), with the exclusion of those patients who died during the follow-up period.

At six months of treatment, complete response was seen in 36.7%(n=11) in the cyclophosphamide group and only in 27.3% of patients in the MMF group, but this difference was not statistically significant. (P=0.614). At the end of one year, the complete response was seen in only 56.7 % in the cyclophosphamide group and 81.8 % in the MMF group; however, this difference was also not statistically significant(p=0.282) Though initial response was better with cyclophosphamide and later in MMF group, these were not statistically significant. In the study by Dhir et al.[1]. at the end of one year, out of 130 patients, 71 patients (54.62%), partial remission was seen in 39 patients (30%).In our study, overall, at six months, the complete response rate was 34.78% (16 out of 46 including those on prednisolone only), and the partial response rate was 52.17%.

At the end of our study, i.e., after one year, the complete response was seen in 60.87% (28 out of 46 patients including those on prednisolone only), and partial response seen in 30.43 %(14 out of 46 patients). The result of our study is similar to that seen in Dhir et al. group with a slightly higher response rate may because our study is prospective and only 50 patients studied as compared with the above study, which is retrospective and contained relatively large number of patients. The most common complication being tuberculosis or reactivation of latent TB. Therefore each patient should be screened for underlying tuberculosis before starting an immunosuppressant. Also, pancreatitis was quite common.

Therefore abdominal pain in the case of SLE should be investigated for pancreatitis. The complication has been seen most commonly in the patient treated with cyclophosphamide 83.33 % (n=12) than that of MMF 16.67%(n=2). Therefore one should be considered the risk-benefit ratio and patients affordability before initiating inductions. Among the 3 patients who died, the causes were: reactivation of underlying tuberculosis in one patient (had class III LN), pneumonia with septicemia in one patient (had class IV LN), one death of severe disease activity at presentation (biopsy was not done). In the study by Dhir et al.[1].

Among the 16 patients who died, the causes were infections in 8 (sepsis in 4, disseminated tuberculosis in 3, and pneumonia in 1), subdural hematoma in 1 (on anticoagulation), severe bone marrow aplasia with pulmonary hemorrhage in 1, acute abdomen in 1 (unknown cause), post-surgery Sudden death in 1, diabetic ketoacidosis in 1, suicide in 1, and unknown in 2 (1 of whom was in renal failure). In the study by Cevera R et al. "Morbidity and mortality in systemic lupus erythematosus during 10 years: a comparison of early and late manifestations in a cohort of 1,000 patients", the most frequent causes of death were active SLE(26.5%), thrombosis(26.5%) and infections(25%) with active SLE and infections appeared to be a most common cause of death during initial 5 years period while thrombosis became a most common cause of death during last 5 years.[2]. As a developing country, the main cause of death being infection which correlated with other Indian studies.

Conclusion

Treatment with either CYP or MMF is equally effective, but underlying infection, particularly tuberculosis, should be ruled out before starting therapy.

What does the study add to existing knowledge?

Therapy with either CYP or MMF is equally effective in the treatment of Lupus.

Author contributions

TD, AR collected the data and conducted this study. RP and TD did data analysis. TD, AR and RP did manuscript drafting. All authors were involved in revising and approved the final version of the manuscript.

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