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A Study on Pharmacotherapeutic Management in Patients with Lupus Nephritis with Immunosuppressants

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Abstract

Aim: To address the adverse drug reactions associated with all the drugs involved in treatment plan which include immunosuppressants. **Methods:** A Retrospective observational study was carried out in Nephrology department at Sri Venkateswara Institute of Medical Sciences. This study mainly focuses on pharmacotherapy of lupus nephritis as induction and maintenance therapy with immunosuppressants and corticosteroids. There is a chance of adverse drug reactions with the therapeutic regimens. So, these reports were also analyzed for adverse drug reactions, causality, severity and preventability assessment. **Results:** A total of 75 patients were included in our study. Patients with clinical features of lupus nephritis satisfying at least 3 of ARA criteria for Systemic lupus erythematosus and diagnosed at the time of renal biopsy were included. The mean age at presentation was (31.02±11.09). Majority members were females (m: f= 1:5). Pedal edema (48%), decreased urine output (17.33%), shortness of breath (16%) is mostly observed adverse drug reactions in our study. The patients were hypertensive (25.33%) and hypothyroidism (10.66%) at the time of presentation. WBC count (7553.93±4266.98), proteinuria (562.8±904.07), serum creatinine (1.64±1.41), serum albumin (2.70±1.47), C3 (22.22%), were estimated in 6 month's study. Majority belonged to class IV (56%) and class V (10.66%) lupus nephritis. **Conclusion:** Lupus nephritis is common in female gender in the adult age group with multi system manifestations secondary to immunological involvement (ds DNA) as substantiated in our study. The disease management requires corticosteroids, cyclophosphamide, mycophenolate mofetil at different stages for the control of immunological activity as substantiated in our patient group.

Keywords
Systemic lupus erythematosus, lupus nephritis, cyclophosphamide, mycophenolate mofetil, prednisolone.

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INTRODUCTION:

Systemic Lupus Erythematosus is a heterogeneous autoimmune disease which is characterized by the production of multiple auto antibodies in the blood and affects many organs including the skin, joints, central nervous system and kidney [1]. The incidence rate around the world is about 1 to 10 /100,000 population/year and the prevalence rate range from 20-70/100,000 population/year [2]. The clinical features of systemic lupus erythematosus are fatigue, weight loss, fever, anemia, Arthralgia [3]. Lupus Nephritis is one of the complication of systemic lupus erythematosus [4].

Lupus nephritis is an immune complex glomerulonephritis that is common and serious feature of systemic lupus nephritis [5]. Inflammation of the nephrons the structure within the kidney that filters the blood is called nephritis. Lupus nephritis is the term used when lupus causes inflammation in your kidneys making them unable to properly remove waste from your blood or control the amount of waste in your body [6]. The incidence rate of lupus nephritis were 3- 8 times higher in blacks, 3.7 in Asians, 2.3 in native Americans and 1.9 in Hispanic [7]. The most common clinical manifestations include proteinuria, Hematuria, Hypertension, reduced glomerular filtration rate, renal tubular function is often disturbed, resulting in urinary excretion of Tamm-Horse fall proteins [8]. The diagnostic tests include urine tests, blood tests, imaging tests such as ultra sound, kidney biopsy and 24 hour's urine collection [9].

Table 1: ISN/RBS (2003) classification of lupus nephritis [10].

S.NO.	CLASS	TYPE
1	Class-1	Minimal mesangial lupus nephritis
2	Class-2	Mesangial proliferative lupus nephritis
3	Class-3	Focal lupus nephritis
4	Class-4	Diffuse lupus nephritis
5	Class-5	Membranous lupus nephritis
6	Class-6	Advanced sclerosis lupus nephritis

Treatment:

The current widely accepted treatment regimens for lupus nephritis incorporate corticosteroid (prednisolone) with cyclophosphamide as induction therapy and prednisolone with Mycophenolate mofetil as maintenance therapy in order to control inflammation and autoimmunity [11].

AIM:

The current study deals with the nature of lupus nephritis with immunosuppressants management. Apart from lupus nephritis, this study also aims to address the adverse drug reactions associated with all the drugs involved in treatment plan which include immunosuppressants.

MATERIALS AND METHODS:

A retrospective observational study of a data retrieved from medical records of lupus nephritis patients was carried out in the department of nephrology, Sri Venkateswara Institute of Medical Sciences, Tirupati from August 2018 to January 2019. This study was approved by institutional ethics committee (Roc. No. AS/11/IEC/SVIMS/2017). The medical records are scrutinized to evaluate the pharmacotherapy among lupus nephritis patients of either sex and gender of all age groups. After scrutiny of the available medical records since January 2012 to January 2019, data of 75 patients met the inclusion criteria. A structured patient data collection form was used to collect the patient details like age, past medical history, past medication history and other co-morbid conditions, diagnostic parameters of lupus nephritis and immunosuppressive therapy. This study mainly focuses on the immunosuppression therapy as induction and maintenance therapy which is achieved by either single immunosuppressant or combination of two drugs along with a single corticosteroid. There is always a chance for ADRs associated with therapeutic regimens. The nature of adverse drug reactions was collected and recorded in suspected adverse drug reactions reporting form designed by Indian Pharmacopoeia Commission

under pharmacovigilance programme of India. The assessment of causality, severity and preventability of adverse drug reactions by using World Health Organization-Uppsala monitoring center (WHO-UMC) scale, Naranjo's scale, Modified Hart wig and Siegel severity scale, Modified Schumock and Thorton's preventability scale, respectively. A descriptive analysis of the data was done using Microsoft Excel 2013 and results were expressed as numbers and percentage.

RESULTS:

The available data from medical records of 75 lupus nephritis patients suggests that 47 of 75 patients fall under age group of 21-40 years, 16 patients between ≤20 age group, 11 patients between 41-60 age group and 1 patient fall under age group of ≥60. 63 out of75 patents are females and rest of 12 are males. Based on the disease characteristics predominant class of lupus nephritis was class IV (60.31%) in women and class IV and V with equal distribution in men (33.33%). According to the laboratory parameters Anemia, elevated ESR, renal dysfunction, hepatic enzymatic, hyperlipidemia, hyponatremia, hypokalemia, urine evaluation is suggestive of nephritic and nephrotic presentation with significant proteinemia. Patients had arthralgia 20 (26.66%), Hypertension 19 (25.3%), and hypothyroidism 8 (10.66%) has been predominantly noted co morbidities. The maximum and minimum number of adverse drug reactions have been reported in lupus nephritis patients who have used the single drug prednisolone (47.36%) followed by cyclophosphamide (11.27%) followed by mycophenolate mofetil (9.02%) and in combination drugs cyclophosphamide + prednisolone (15.78%) followed by mycophenolate mofetil + prednisolone (12.03%) and the remaining are listed in Table 5.

Table2: Baseline disease characteristics of lupus nephritis patients

Gender	WHO classes										
	I	II	III	IV	V	II, III	II, IV	III, IV	III, V	IV, V	II,IV,V
Female (63)	2(3.1%)	5(7.9%)	3(4.7%)	38(60.3%)	4(6.3%)	-	1(1.5%)	3(4.76%)	1(1.5%)	5(7.93%)	1(1.58%)
Male (12)	-	2(16.6%)	-	4(33.3%)	4(33.3%)	1(8.33%)	-	-	-	1(8.3%)	-

a) Table 2 shows the predominant class of lupus nephritis was class IV in women and class IV and V with equal distribution in men.

Table3: Baseline laboratory values in lupus nephritis patients

Characteristics	Female (63)	Male (12)
Hemoglobin(g/dl) (↓)	51 (80.9%)	8 (66.6%)
ESR (mm/1sthr) (↑)	38 (60.31%)	6 (50%)
Serum albumin(g/dl) (↓)	22 (34.92%)	4 (33.33%)
Serum creatinine(mg/dl) (↑)	33 (52.38%)	5 (41.66%)
SGOT (↑)	9 (14.28%)	3 (25%)
SGPT (↑)	7 (11.11%)	2 (16.66%)
Sr. cholesterol(mg/dl) (↑)	9 (14.28%)	1 (8.33%)
Triglycerides(mg/dl) (↑)	14 (22.22%)	5 (41.66%)
Sodium(mmol/L) (↓)	9 (14.28%)	1 (8.33%)
Potassium(mmol/L) (↓)	10 (15.87%)	2 (16.66%)
Total urine protein (g/24 hrs)(↓)	40 (63.49%)	6 (50%)
Urine creatinine(mg/24hrs)	24 (38.09%)	2 (16.66%)
Sediments:		
RBC(hpf)	30 (47.61%)	1 (8.33%)
Pus cells(hpf)	28 (44.44%)	2 (16.66%)
Epithelial cells(hpf)	21 (33.33%)	1(8.33%)

b) The laboratory parameters were suggestive of Anemia, elevated ESR, hypo, renal insufficiency (renal dysfunction), hepatic enzymatic, hyperlipidemia, hyponatremia, hypokalemia, urine evaluation is suggestive of nephritic, nephrotic presentation with significant proteinemia.

Figure: 1 Co morbidities in patients with lupus nephritis

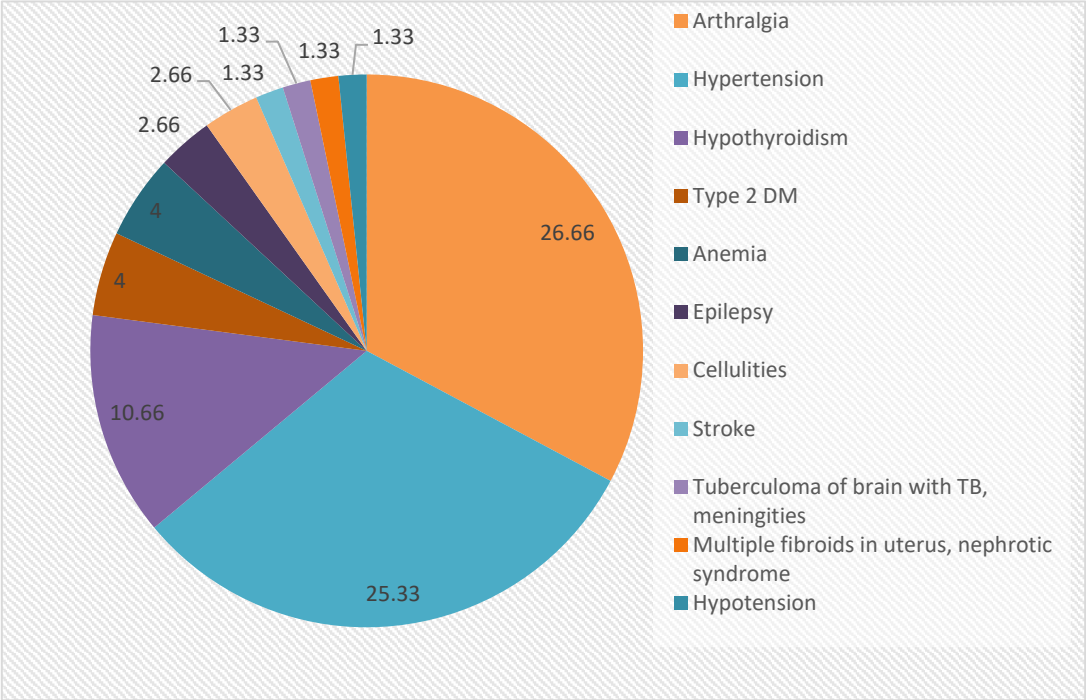
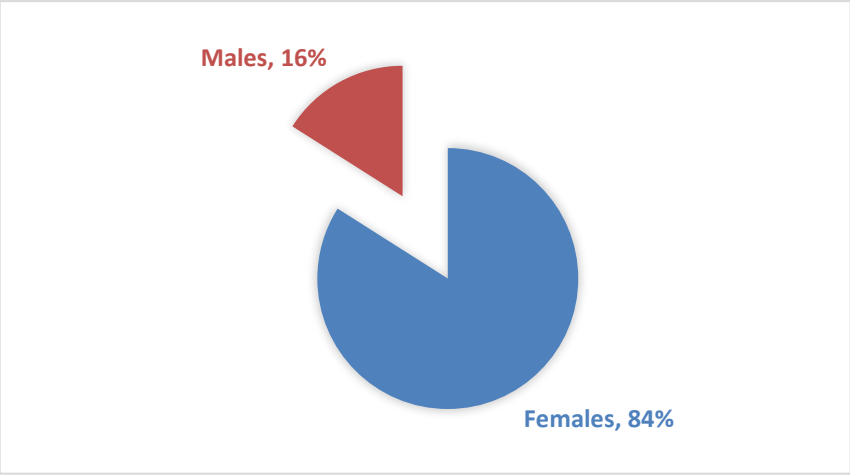


Figure: 2 Gender wise distribution



Gender wise distribution showing disease predilection is seen more in females in comparison to males.

Table5: Age wise distribution of lupus nephritis patients with ADRs

Age (yrs)	No. of patients with ADRs in LN (54)	Percentage (100)	No. of patients without ADRs LN (21)	Percentage (100%)
≤ 20	12	22.2%	4	19.0%
21-40	32	59.25%	15	71.4%
41-60	9	16.6%	2	9.5%
≥60	1	1.85%	0	0

c) With regard to adverse drug reactions are more in adult age groups followed by young and middle age groups respectively.

Table 6: Incidence of adverse drug reactions.

Suspected Medication	Parameters (All Adverse drug reactions)																			Total/ percentage
	SOB	PE	WL	BV	F	UO	LA	HA	V	C	A	AD	LB	P	R	HL	CP	HU	FP	AG	(100%)
P	8	19	1	2	2	8	3	-	2	2	2	5	-	-	1	3	-	-	5	-	63(47.36%)
CYC+P	4	3	-	-	-	-	3	-	-	-	2	1	1	1	2	3	-	1	-	-	21(15.78%)
MMF+P	-	7	-	-	1	2	-	1	-	-	-	3	-	-	-	1	-	-	1	-	16(12.03%)
CYC	-	4	-	-	2	-	-	-	-	1	-	-	-	-	1	1	-	2	-	4	15(11.27%)
MMF	-	2	1	-	1	3	-	1	1	1	-	-	-	-	-	1	1	-	-	-	12(9.02%)
CYC+MMF	-	1	-	-	2	-	-	-	-	-	1	-	-	-	-	1	-	-	-	-	5(3.75%)
CYC+MMF+P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1(0.75%)
TOTAL	12	36	2	2	8	13	6	2	3	4	5	9	1	1	4	11	1	3	6	4	133

P-prednisolone, CYC+P – Cyclophosphamide+ Prednisolone, MMF+P -mycophenolate mofetil+ Prednisolone, CYC – Cyclophosphamide, MMF – Mycophenolate mofetil, CYC+MMF – Cyclophosphamide+ Mycophenolate mofetil, CYC+MMF+P – Cyclophosphamide+ mycophenolate mofetil+ Prednisolone.
SOB - Shortness of breath, PE - Pedal edema, WL - Weight loss, BV - Blurred vision, F- Fever, UO- Decreased urine output, LA - Loss of appetite, HA - Headache, V- Vomiting, C- Cough, A- Anemia, AD- Abdominal distension, LB - Lower back pain, P- Pancytopenia, R- Rashes, HL- Hairloss, CP- Chest pain, HU- Hematuria, FP- Facial puffiness, AG- Arthralgia.

Table6: Severity of Adverse drug reactions

Reaction	Mild	Moderate	Severe
Pedal edema	22	14	
Decreased urine output	13	-	
Shortness of breath	12	-	
Hair loss	6	5	
Abdominal distention	8	1	
Fever	8	-	
Facial puffiness	3	3	
Loss of appetite	6	-	
Anemia	-	5	
Rashes	2	2	
Arthralgia	2	2	
Vomiting	1	2	
Hematuria	3	-	
Cough	3	-	
Weight loss	2	-	
Blurred vision	2	-	
Head ache	2	-	
Chest pain	1	-	
Lower back pain	1	-	
Pancytopenia	-	1	
TOTAL	98 (73.68%)	5 (26.31%)	0

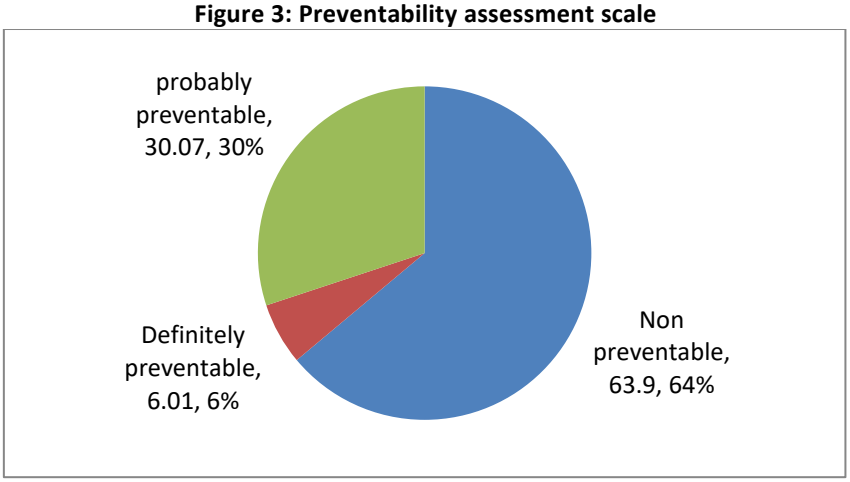
e) This table shows the severity of adverse drug reactions by modified Hart wig and Siegel scale, out of 133 adverse drug reactions were found to be mild 98(73.68%), 35(26.31%) adverse drug reactions were moderate.

Table7: Causality Assessment of ADRs by Naranjo's scale and WHO scale

Parameters	No. of ADRs	
	Naranjo's scale	WHO scale
Definite	0(0%)	0 (0%)
Probable/ likely	19 (14.28%)	90 (67.66%)
ossible	114 (85.71%)	43 (32.33%)
Doubtful/Unclassified	0 (0%)	0 (0%)
TOTAL	133	

f) Naranjo's and WHO causality assessment scale revealed 90(67.66%) ADRs were probably related to Immunosuppressant therapy and 43(32.33%) ADRs were possibly related.

Figure 3: Preventability assessment scale



Preventability assessment by modified schumock and Thornton Scale, 85 adverse drug reactions were non preventable, 40 adverse drug reactions were probably preventable, 8 are definitely preventable.

DISCUSSION:

Systemic lupus erythematosus is an autoimmune disease in which diverse immunological events can lead to a similar clinical picture, characterized by a wide range of clinical manifestations and target organs with unpredictable flares and remission that eventually lead to permanent injury. Socio demographic factors such as sex, race and ethnicity play an important role in the incidence of the disease, frequency of its manifestations and therapeutic response. The overall prevalence and incidence of systemic lupus erythematosus ranges from 1.4 to 21.9% and from 7.4 to 159.4 cases per 100 thousand people respectively. Systemic lupus erythematosus can affect several organs and systems including the joints, skin, brain, heart, lungs, blood vessels and kidneys.

Lupus nephritis is almost serious systemic lupus erythematosus since it is the major predictor of poor prognosis, the lupus nephritis cumulative incidence is higher in Asian (51%), Africans (51%) and Hispanic (43%) in comparison with Caucasians (14%). About 25% of these patients develop End stage renal disease(ESRD) 10 years after onset of renal compromise. Lupus nephritis looked upon as a classic example of immune complex induced microvascular injury which results from circulating double stranded DNA, polynucleotide antigens/anti DNA antibody complexes and other mechanisms including insitu for free antibodies with fixed antigens and presence of sensitized T cells which are an important part of the picture.

Immune complex glomerular deposits generate release of pro inflammatory cytokines and cell adhesion molecules causing inflammation. This leads to monocytes and polymorphonuclear cells chemotaxis. Subsequent release of proteases generates endothelial injury and mesangial proliferation. Presence of ICs promotes adaptive immune response and causes dendritic cell store

release type I interferon. This induces maturation and activation of infiltrating T cells, and amplification of Th2 and Th1 and Th17 lymphocytes. Each of them, amplify B cells and activates macrophages to release more pro inflammatory molecules generating effector cells that cannot be modulated promoting kidney epithelial proliferation and fibrosis [12].

Keeping in view of a serious nature of this entity early recognition, diagnostic confirmation, effective therapeutic management and regular periodic follow up is mandatory for gratifying outcomes in terms of remission morbidity and mortality.

In the light of above discussion, we here discuss our observations obtained from our data. This study included 75 patients of lupus nephritis treated in the department of nephrology, Sri Venkateswara institute of medical sciences. Our study duration was 6 months (August 2018 to January 2019).

The patient population in our study group belong to the range 8 to 73 years, about 66.66% were in adult age group majority 84% of patients belong to female gender. Our observations were in concurrence with the observations from the existing literature.

The male: female ratio in our study group was (1:5) emphasizing that predominant occurrence in the female gender as reported in the literature.

The BMI distribution between the genders is almost similar in our study. However, on further analysis we found in males, the BMI distributions are different between the genders. In male's normal weight 50%, over weight 25% and obese 25% in females underweight 25%, normal 42%, over weight 11%, obese 22%.

The diagnosis of systemic lupus erythematosus was made in taking the help of American college of Rheumatology (ACR) criteria for diagnosis of lupus. The diagnosis of lupus nephritis was made keeping in view of clinical picture, urine examination, immunological assay, proteinuria, renal function assessment and renal histopathology. Based on International Society of Nephrology/ Renal pathology Society [ISN/RPS] classification for lupus nephritis the various renal histopathological observation in light microscopy and immunofluorescence [13].

In our study group we found class IV (n=38) as the predominant in females constituting about (60.31%) in comparison to the other class all (n=25) put together (40%). In our study male (n=12) population we observed predominantly class IV and class V with equal distribution (n=4, 33.33%) patients in each group.

Keeping the complete data in view we observe class IV group is the dominating one (56%) followed by class V (10.66%). Our observation of the occurrence of class IV and V group of lupus nephritis with class IV predominance is in concurrence with the existing literature.

Table 8: Base line and clinical parameters

S. No.	Parameters	Our study	Satish Mendonca *et al*
1.	Age	31.02±11.09	25±10.55
2.	Gender (male/ female)	12/63	8/32
3.	Hemoglobin	9.35±2.29	-
4.	WBC count	7553.93±4266.98	9.15±4.2($^{\cdot}$$_{109/l}$)
5.	Anti-ds DNA positive	38.6%	47.5%
6.	Serum Albumin	2.70±1.47	2.54±.3
7.	Serum creatinine	1.64±1.41	0.84±1.45
8.	C3 count	22.22%	46.24±1.6
9.	Hematuria	1±0	92.5%
10.	24 hrs Urine protein	562.8±904.07	2.63±2.29

In our observation on the incidence of adverse drug reactions reported during the disease management compared with the study data from Gerald B. Appel *et al* we found edema, rash, abdominal distension was higher in our patient group while arthralgia, alopecia, cough, headache, lower back pain was low in comparison. The same was tabulated in table (5).

In our study group we found hypertension, hypothyroidism and arthritis as predominant comorbidity while the rest of the entities were

constituted small percentages. The data was represented in figure (1)

In composition to other Indian study in our group we found adult and female predominance were in concurrence. We found a lower value in protein urea, hematuria, anti- ds DNA positivity, C3 positivity. In our group there was mild to moderate anemia and normal total WBC count. Our data was noted in table 8 [14].

Patients of lupus nephritis are treated with corticosteroids (prednisolone), cyclophosphamide and mycophenolate mofetil depending on the response some time they may also be considered for calcineurin inhibitors such as cyclosporin or tacrolimus. In our study group some of the patients were treated with prednisolone and cyclophosphamide induction therapy followed by prednisolone and mycophenolate mofetil as maintenance therapy.

Our group included patients with corticosteroids and mycophenolate mofetil induction therapy followed by maintenance therapy. None of our patients on calcineurin inhibitors a small group were also given azathioprine in place of mycophenolate mofetil as a maintenance treatment when patients didn't tolerate MMF.

The drugs that are used to treat lupus nephritis condition in our study are prednisolone, cyclophosphamide, mycophenolate mofetil. The mostly reported ADR is seen in the drug prednisolone with an adverse drug reaction pedal edema. The least ADR is seen the combination of drug prednisolone + cyclophosphamide + mycophenolate mofetil with an adverse drug reaction alopecia.

Some adverse drug reactions like vomiting, rashes, loss of appetite, fever, lower back pain, blurred vision etc. which we have observed in our study are considered to be non-serious. Based on severity scale [15], the adverse drug reactions which are reported in the patients with lupus nephritis conditions, in our study are mild (73.68%) and moderate (26.33%) there are no severe adverse drug reactions reported.

The maximum and minimum number of adverse drug reactions have been reported in lupus nephritis patients who have used the single drug prednisolone (47.36%) followed by cyclophosphamide (11.27%) followed by mycophenolate mofetil (9.02%) and in combination drugs cyclophosphamide + prednisolone (15.78%) followed by mycophenolate mofetil + prednisolone (12.03%) followed by cyclophosphamide + mycophenolate mofetil (3.75%) followed by cyclophosphamide + mycophenolate mofetil + prednisolone (0.75%).

The adverse drug reactions that are reported in the lupus nephritis patients in our study are mostly probable (based on WHO scale 66.66%, based on Naranjo's scale14.28%) and possible (based on WHO scale 32.33%, based on Naranjo's scale 85.71%) [16, 17].

From our study the adverse drug reactions that are reported in patients with lupus nephritis are definitely preventable (6.01%) followed by probably preventable (30.07%) followed by not preventable (63.90%) with respect to preventability assessment by modified schumock and thornton scale [18]. Anemia can be prevented by undergoing blood transfusion and by taking drugs like Nefita and tablet folic acid and following life style modifications.

Limitations of our study include lack of data regarding patient demographic details and incomplete information on laboratory investigations.

CONCLUSION:

Lupus nephritis is common in female gender in the adult age group with multi system manifestations secondary to immunological involvement (ds DNA) as sustained in our study. The disease management requires corticosteroids, cyclophosphamide, mycophenolate mofetil at different stages for the control of immunological activity as sustained in our patient group. Causality, severity, preventability was assessed with specific scales as a part of exercise in the part of study group. Most of the adverse drug reactions are noticed with prednisolone and least adverse drug reactions are noticed with mycophenolate mofetil. It is hoped that more treatment options can be offered to patients with class IV and V lupus nephritis in the future, and the prognosis of the condition can continue to improve.

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