

Use Of Rituximab In The Treatment Of Lupus Nephritis In Compares To Cyclophosphamide: A Prospective Cohort Study In Single Center Institution.

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ABSTRACT

Lupus nephritis is one of the major manifestations of systemic lupus erythematosus and is responsible for a substantial disease associated with morbidity and mortality. Treatment of it limited by the lack of effective treatment and side effects of the currently available immunosuppressive regimens; this led to a search for other therapeutic agents with potential for the better therapeutic outcome and less side effects like anti CD 20, rituximab. To assess rituximab's efficacy in inducing renal remission in a patient with lupus nephritis compared to cyclophosphamide. Thirty-nine subjects with biopsy-proven lupus nephritis and active disease, divided into two groups, rituximab group (26 patients) and cyclophosphamide group (13 patients), the first group designated to receive rituximab at a dose of 375 mg/m² every two weeks for a total of 6 doses, and cyclophosphamide group designated to receive cyclophosphamide IV at a dose of 500 mg/m² every month for a total of 6 cycles. Patients were evaluated every three months for clinical improvement in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score and renal response achievement for a total of 3 visits (9 months). There was no difference in age or disease duration between 2 groups; disease activity was higher in the cyclophosphamide group. Cyclophosphamide achieved clinical response at nine months, (reduce SLEDAI score from 15.9 to 2.7), while rituximab achieves only partial clinical response (SLEDAI score from 12 to 6). Cyclophosphamide reduces proteinuria from 133 mg/mmol at baseline to 31 mg/mmol at 9 months, while for rituximab from 92 mg/mmol to 67 mg/mmol, at nine months, the complete and incomplete renal response in (84.6%) of patients on cyclophosphamide and in (50%) of patients treated with rituximab, non-responder and relapse seen in (15.4%) of patients treated with cyclophosphamide while in (50%) of those treated with rituximab. (P value=0.036). Cyclophosphamide is more effective than rituximab in inducing remission in patients with Lupus nephritis.

Keywords: Lupus nephritis; SLE, cyclophosphamide; rituximab; immunosuppression regimes

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INTRODUCTION

The systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder of unknown aetiology [1]. It characterized by autoantibody production against an intracellular antigen of which the antinuclear antibodies are most prevalent [2]. It is primarily a disease of females of child-bearing age with female to male ratio of 9:1, its prevalence in Iraq is (50/100000), in Saudi Arabia is (19/100000), in Iran is (40/100000) of the population [3], and in united states ranging from (15-200/100000 women) with the highest prevalence among African-American and Afro-Caribbean [4], Lupus nephritis (LN), heterogeneous group of disorder, in which all four renal compartments (the glomeruli, tubules, interstitium, and blood vessels) may be affected. Immune deposits detected in any or all renal compartment [5]. Renal involvement is one of the more serious manifestations of SLE and is associated with increased morbidity and mortality. The features most commonly seen in patients with lupus nephritis are proteinuria, urinary casts, hematuria, pyuria, a rising serum creatinine value and hypertension. Renal biopsy is essential in determining the type of kidney involvement, which correlates with severity, prognosis, and treatment determination [6]. The World Health Organization classification in 2004 used to classify renal involvement, in which class I and II considered to be a relatively benign lesion, do not require aggressive immunosuppressive therapy and do not

progress to permanent renal damage. Class III and Class IV (the most common) are the most severe form of lupus nephritis, characterized by subendothelial deposits and carry a high risk of progression to permanent renal damage in the future and require aggressive immune suppressive therapy to halt this sequel. Membranous lesions (class V) have mainly subepithelial deposits and may exhibit mesangial involvement. Advanced sclerosis (class VI) is considered the end stage of all the other lupus nephritis classes [7]. The flare of lupus nephritis occurs in 27-66% of patients with class IV tend to relapse more frequently than others [8]. Lupus nephritis and infection are the two major causes of death in a patient with SLE in the first ten years of the disease. If patients with class IV diffuse proliferative glomerulonephritis inadequately treated, most of them will develop the end-stage renal disease (ESRD) within two years of diagnosis [9]. For this reason patients with class III, IV lupus nephritis is treated aggressively with initial pulse steroid (Methylprednisolone 500-1000 mg for three days) followed by 0.5 mg/kg/day for 4-6 weeks then taper combined with immunosuppressive therapy either iv cyclical cyclophosphamide or mycophenolate mofetil (MMF). Cyclical cyclophosphamide (CYC) was superior to steroid alone in achieving renal remission and prevention of further relapse [10] CYC side effects include nausea, vomiting, infection, leucopenia, hair loss, gonadal failure (age and dose-related), hemorrhagic cystitis, bladder

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cancer.[11] After induction of remission; a maintenance therapy started with the aim to maintain remission, prevent relapse or reduce the severity of relapse and it is consist of long term corticosteroid with the lowest possible dose combined with other immunosuppressive therapy likeMethiopropamine (MPA), MMF, azathioprine, tacrolimus and cyclosporine for 2-3 years according to the severity of lupus nephritis with the best evidence is for MMF and Azathioprine (AZA).[12,13] Till now and despite the advances in immunosuppressive regimen, rates of ESRD over 5–10 years are in the range of 10%, a percentage that has still constant over the previous 30 years in the united states.[14] In addition to many side effects related to long term steroid use and other immunosuppressive therapy like gonadal toxicity, risk of malignancy, and teratogenicity, These factors collectively had clarified the need for a more effective treatment for lupus nephritis with less side effect which has led to the explorative use of rituximab (anti CD20) in the treatment of lupus nephritis. Rituximab therapeutic B-cell depletion with monoclonal antibodies originally developed as a treatment of B-cell malignancies and is now used to manage several rheumatic diseases. [15] Rituximab the first anti-CD20 monoclonal antibody used in the clinical practice consists of the fusion of the light- and heavy-chain variable regions of a murine antihuman monoclonal anti-CD20 antibody with human immunoglobulin κ light-chain and γ 1 heavy-chain constant regions. [16] Safety of rituximab use patients should screen for chronic cardiopulmonary disease, active infection, pulmonary tuberculosis [17] and hepatitis B virus infection. An infusion reaction is the most common side effect, more marked in the first dose, and may be related to the speed of infusion, occur at a rate of 37% like fever, itching, urticarial and sore throat. Serious side effects like anaphylaxis and bronchospasm are much less common < 1%. Infusion reactions treated with paracetamol, antihistamine, and steroid. [18] Cyclophosphamide (CYC) It is an alkalinizing agent that is metabolized by the liver to its active ingredient phosphoramidate mustard, which acts by inducing cross-linking of DNA so make it unable to replicate. [19] CYC is toxic to both dormant and proliferating lymphocyte. It affects both T- cells and B-cells. [20] Another metabolite of CYC is the acrolien, which is responsible for the bladder toxicity of CYC, which can be prevented by the co-administration of MESNA drug. [21] CYC and its metabolites secreted through the kidney. Till recent years, CYC was the treatment of choice for lupus nephritis (particularly WHO class III and class IV). CYC used for induction therapy at doses (500-750 mg/m²) on monthly bases for six months, followed by maintenance therapy [22]. The most important factor that affects CYC use is the Side effect profile of CYC which include well known serious manifestation like increased risk of non-Hodgkin lymphoma and bladder carcinoma, hemorrhagic cystitis [23], marrow suppression, infection, herpes zoster, teratogenicity, gonadal failure, hair loss, mucositis, nausea and vomiting. [24]

PATIENTS AND METHODS

A prospective cohort study conducted in the Nephrology unit of AL Sader medical city between January 2019 and December 2020. Inclusion criteria

- Patient meeting at least 4 of the American college of rheumatology diagnostic criteria of SLE.
- Aged 15-65 years.

- Has biopsy-proven lupus nephritis with histologic class II, III, IV.
- Active disease with SLEDAI-2k score 1 of 4 or more at the time of entry.
- All patients were receiving corticosteroid then oral maintenance therapy with mycophenolate mofetil or azathioprine, with doses adjusted as clinically indicated.

Exclusion criteria:

- Age >65 or <15 years.
- Lupus nephritis class I, V, or VI on renal biopsy.
- Patient requiring regular dialysis for more than one month.
- Transplanted kidney.
- SLEDAI-2K score equal to or less than three at the time of entry.
- Patient with active infection or latent TB, not on treatment.
- Patients who are positive for HBV, HCV or HIV.
- Pregnant ladies.
- For rituximab arm patient who previously received cyclophosphamide.
- For cyclophosphamide arm patient who previously received rituximab.

Data collected from each patient include age, gender, race, body weight, height, smoking status, past medical history (hypertension, diabetes, IHD, heart failure) and disease duration. Forty-five patients evaluated, six patients were excluded (2 with age below 15 years, 2 had class V lupus nephritis, 2 had the inactive disease). 39 patients included eligible patient divided into two groups: rituximab group and cyclophosphamide (CYC) group, in 2:1 ratio each patient has biopsy-proven lupus nephritis class II, III, and IV according to WHO classification of lupus nephritis 2004, either as a first manifestation or as the flare of the disease, with each patient having active SLE as assessed by (SLEDAI-2K) score,[25] a score equal to or more than four required at time of entry, each patient had urine sample assessed for the presence of any RBC cast, and urinary protein/creatinine ratio (PCR) > 50 mg/mmol, done by QuantiChrom™ Protein Creatinine Ratio Assay kit and measurement of S. creatinine at the time of entry. Rituximab group designed to receive 375 mg/m² of rituximab every two weeks for six doses. Patients also received a standard dose of pulse steroid (500-1000 mg of MP) at the initiation of therapy as per guidelines. Each dose of rituximab was premeditated by paracetamol (500-1000mg), chlorpheniramine (10 mg) and hydrocortisone (100 mg). Cyclophosphamide group designed to receive IV cyclophosphamide (500 mg/m²) on monthly bases for six months; Patient also received a standard dose of pulse steroid (500-1000 mg of MP) at the initiation of therapy as per guidelines. [22] All patients received oral therapy with prednisolone (0.5- 1 mg/kg) for four weeks then taper to lowest possible dose, with oral maintenance therapy in the form of mycophenolate mofetil (20-30 mg/kg/day) or azathioprine (1-2.5 mg/kg/day) added after completion of iv therapy and adjusted as clinically indicated [22]. Other medication like antimalarial, ACE inhibitor, angiotensin receptor blocking (ARB), was continued. Patients were evaluated every three months for three visits. In each visit, disease activity assessed using SLEDAI-2K [25] and SLEDAI-2K responder index-50 to measure disease activity improvement.[26] A urine sample examined for urine PCR, and RBC cast and serum creatinine measured. A questionnaire for rituximab side

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effect provided with each infusion of rituximab to assess its side effects. Study target:

-Overall improvement in disease activity by SLEDAI-2K was: score of 3 or less indicates disease in remission. Reduction of SLEDAI-2K by > 50% using SLEDAI-2K responder index-50 indicate a partial clinical response.

-Renal response target were:

Complete renal response (CRR): all of the following:

-PCR <50 mg/mmol.

-absent cast.

-Stable or reduced s. creatinine.

Incomplete renal response (IRR): Patients achieve improvement in 2 of the following parameters without others' worsening.

-Reduction in PCR > 50% from baseline.

-Reduction in RBC cast > 50% from baseline.

-Stable s. creatinine or improving.

Non-responder (NR): patient not achieving 50% reduction in PCR, RBC, RBC cast or s. creatinine, although partial clinical response. Renal relapse (RR): worsening of PCR, RBC, RBC cast, or s. creatinine by more than 50% after achieving complete or partial response with clinical deterioration. [27] Refractory lupus nephritis: describe

persons with lupus nephritis who show no or partial response to 1st line therapy (CYC and MMF). [28]

Statistical Analysis

SPSS Software version 23.0 used to perform statistical analysis. Qualitative data presented as number and percentage and continuous numerical data presented as mean ± standard deviation. Comparison of study groups was carried out using the chi-square test for categorical data and using Student's t-test for continuous data. P-value of < 0.05 was considered statistically significant.

RESULTS

The age for rituximab group was 25.4± 7.5 years, and for CYC group, it was 25.5± 7.5 years, 26 (100%) of the rituximab group were females. In contrast, 11 (84.6%) of the CYC group. 2 (7.7%) patient of the rituximab group had diabetes while 1 (7.7%) patient for CYC group. Disease duration was 19 ± 11.4 months for rituximab group and 13.3 ± 9.3 months for CYC group (P = 0.126) not significant. The demographic characteristic of the study groups compared in the table (1) Age group distribution summarized in figure (1).

Table 1: Demographic characteristics of the participants

Characteristics	Rituximab Group (n=26)	Cyclophosphamide Group (n=13)	P-value
Age (years)	25.4 ± 7.5	25.5 ± 7.4	0.952
Gender (Female)	26 (100%)	11 (84.6%)	0.040*
BMI (kg/m ²)	25.7 ± 1.8	26.2 ± 2.3	0.412
Hypertension	6 (23%)	4 (30%)	1.000
DM	2 (7.7%)	1 (7.7%)	1.000
Smoking	(0.0%)	0 (0.0%)	1.000
Disease Duration (months)	19.0 ± 11.4	13.3 ± 9.3	0.126
Race (Arab)	26 (100%)	13 (100%)	1.000

The study groups' clinical and biochemical characteristics showed the following: SLEDIA score was (12+ 2.8) for the rituximab group and was (16+ 2.9) for CY group. PCR was (92+ 42) (mg/mmol) for rituximab and (132.5+ 50.5) (mg/mmol) for CY group. S. creatinine was (1.29+ 0.55) (mg/dl) for rituximab group and was (0.90+ 0.21) (mg/dl)

for CY group. Other Clinical and biochemical characteristics of the study groups including serum albumin, blood haemoglobin level, WBC, platelets, blood pressure, Previous treatments and Baseline renal biopsy class summarized in table (2).

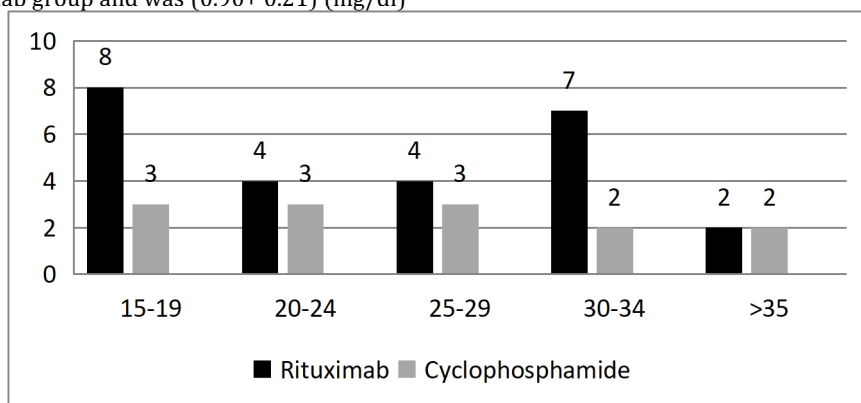


Figure 1: Age distribution of the study subjects

Cyclophosphamide (CYC) was more effective in inducing clinical response, with a decrease in the mean SLEDAI score from 16 to 2 points, and from 12 to 6 points in the rituximab group (P=.004) after approximately nine months of follow up table (3,4). Reduction in SLEDAI score percentage compared to the basal score is illustrated in figure (2). At nine months for rituximab

group 19.2% achieved remission, 30.8% achieved a partial response, and 50% showed no response, while for CYC group, 76.9% achieved remission and 23.1% achieved a partial response, P-value (0.001) which is significant.

Table 2: Baseline clinical and biochemical characteristics of the study groups

Characteristics	Rituximab Group (n=26)	Cyclophosphamide Group (n=13)	P-value
SLEDAI score	12 ± 2.8	16 ± 2.9	< 0.001*

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PCR	92.0 ± 42.0	132.5 ± 50.5	0.012 *
Creatinine	1.29 ± 0.55	0.90 ± 0.21	0.020 *
Albumin	3.83 ± 0.26	3.89 ± 0.45	0.611
Hemoglobin	11.11 ± 1.41	12.32 ± 0.98	0.009 *
WBC count	6177 ± 893	6869 ± 843	0.026 *
Platelet count	230538 ± 46526	238154 ± 39648	0.617
Blood pressure (systolic)	134.5 ± 13.2	140.0 ± 15.3	0.248
(diastolic)	81.2 ± 9.8	82.3 ± 9.3	0.725
Maintenance oral therapy			
Prednisolone	26 (100%)	13 (100%)	1.000
Mycophenolate mofetil	20 (76.9%)	12 (92.3%)	0.238
Azathioprine	6 (23.1%)	1 (7.7%)	0.238
Renal Biopsy Class			
II	5 (19.2%)	0	0.134
III	15 (57.7%)	7 (53.9%)	
IV	6 (23.1%)	6 (46.2%)	

Table 3: Change in the mean SLEDAI score of the study groups

Group	1 st visit (basal)	2 nd visit (after 3 months)	3 rd visit (after 6 months)	4 th visit (after 9 months)
Rituximab	12.0	8.7	6.1	6.0
Cyclophosphamide	15.9	5.5	2.5	2.7
P-value	< 0.001	0.003*	< 0.001*	0.004*

Table 4: Response according to SLEDAI score for 9 months from baseline

Renal Response Category	Group	
	Rituximab (n=26)	Cyclophosphamide (n=13)
Remission	5 (19.2%)	10 (76.9%)
Partial Response	8 (30.8%)	3 (23.1%)
No Response	13 (50.0%)	0
$\chi^2 = 14.18$, d.f. = 2, P = 0.001*		

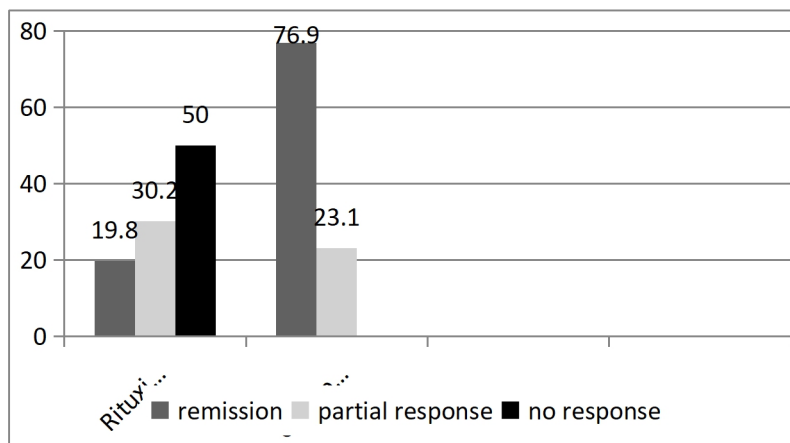


Figure 2: changes in SLEDAI score at 9 months among the subjects. The renal response, rituximab had failed to reduce PCR to > 50% of baseline, at baseline PCR=92 (mg/mmol), at nine months PCR=67 (mg/mmol), while CYC had reduced PCR from 133 mg/mmol at baseline to 31 mg/mmol at nine months. Still, this difference was not

statistically significant (P=0.061), no significant reduction in the number of the cast (P value=0.498), and no significant change in serum creatinine between two groups (P value=0.072) as in table (5,6).

Table 5: Renal response parameters of the study groups

Parameter	Group	1 st visit (basal)	2 nd visit (after 3 months)	3 rd visit (after 6 months)	4 th visit (after 9 months)
PCR	Rituximab	92	76	54	67
	Cyclophosphamide	133	55	29	31
	P-value	0.012*	0.088	0.021*	0.061
Cast	Rituximab	0.42	0.08	0	0.15
	Cyclophosphamide	1.50	0.08	0	0

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	e				
	P-value	0.043	1.0	0	0.498
Serum creatinine	Rituximab	1.29	1.09	0.99	1.00
	Cyclophosphamide	0.90	0.92	0.89	0.89
	P-value	0.020	0.067	0.062	0.072

Table 6: Renal response categories of the study groups over 9 months of follow up

Renal Response Classification	Group	2 nd visit (after 3 months)	3 rd visit (after 6 months)	4 th visit (after 9 months)
Complete renal response	Rituximab	0	5 (19.2%)	3 (11.5%)
	Cyclophosphamide	2 (15.4%)	6 (46.2%)	8 (61.5%)
Partial renal response	Rituximab	7 (26.9%)	8 (30.8%)	10 (38.5%)
	Cyclophosphamide	5 (38.5%)	4 (30.8%)	3 (23.1%)
Non-responder	Rituximab	19 (73.1%)	13 (50.0%)	13 (50.0%)
	Cyclophosphamide	6 (46.2%)	3 (23.1%)	1 (7.7%)
Renal relapse	Rituximab	0	0	0
	Cyclophosphamide	0	0	1 (7.7%)

There was no significant difference in achieving CRR or IRR (overall renal response) between two groups at three months from baseline. Seven patients (53.9%) achieve CRR or IRR for the CYC group, and six patients (46.2%)

show no response. For rituximab group, seven patients (26.9%) achieve CRR or IRR, and 19 patients (73.1%) showed no response, (P value=0.098 not significant) as in the table (7).

Table 7: Overall renal response for the 2nd visit (3 months from baseline)

Renal Response Category	Group	
	Rituximab (n=26)	Cyclophosphamide (n=13)
Complete or incomplete renal response	7 (26.9%)	7 (53.9%)
Non-responder or relapse	19 (73.1%)	6 (46.2%)
$\chi^2 = 2.73$, df = 1, P = 0.098		

There was no significant difference in overall renal response between two groups at six months from baseline; for CY group, ten patients (76.9%) achieve CRR or IRR, and three patients (23.1%) are non-responder.

For rituximab group, 13 patients (50%) achieve CRR or IRR, and 13 patients (50%) are non-responder, (P value=0.107 not significant) result are shown in table (8).

Table 8: Overall renal response for the 3rd visit (6 months from baseline)

Renal Response Category	Group	
	Rituximab (n=26)	Cyclophosphamide (n=13)
Complete or incomplete renal response	13 (50.0%)	10 (76.9%)
Non-responder or relapse	13 (50.0%)	3 (23.1%)
$\chi^2 = 2.60$, df = 1, P = 0.107		

At nine months from the baseline, CYC was more effective than rituximab in achieving CRR and IRR, (P value=0.036), for CYC group, 11 patients (84.6%) achieve CRR or IRR, and two patients (15.4%) show no response or relapse.

For rituximab group 13 patients (50%) achieve CRR or IRR, and 13 patients (50%) are non-responders, (P value= 0.036 significant). as in table (9).

Table 9: Overall renal response for the 4th visit (9 months from baseline)

Renal Response Category	Group	
	Rituximab (n=26)	Cyclophosphamide (n=13)
Complete or partial renal response	13 (50.0%)	11 (84.6%)
Non-responder or relapse	13 (50.0%)	2 (15.4%)
$\chi^2 = 4.39$, df = 1, P = 0.036		

Most of the side effects of rituximab were infusion-related. They included the following: 4 patients (15%) develop itching, two patients (7.7%) develop urticarial, 2 (7.7%) patients develop a sore throat, and 1 (3.8%) patient develops a fever. Serious side effects include: 2 patients (7.7%) develop leucopenia, 1 patient (3.8%)

develops tuberculous lymphadenitis, and 1 patient (3.8%) develops recurrent URTI, for CYC group: 2 patients (15.4%) develop leucopenia, 2 patients (15.4%) develop anemia, 1 patient (7.7%) develop pancytopenia, and 1 patient (7.7%) develop recurrent URTI. Summary of side effects as in table (10).

Table 10: Frequency of side effects in the study groups

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Side effect	Frequency in Rituximab group	Frequency in Cyclophosphamide group
Itching	4 (15.4%)	0
Leucopenia	2 (7.7%)	2 (15.4%)
Urticaria	2 (7.7%)	0
Sore Throat	2 (7.7%)	0
Fever	1 (3.8%)	0
Recurrent URTI	1 (3.8%)	1 (7.7%)
TB Lymphadenitis	1 (3.8%)	0
Pancytopenia	0	1 (7.7%)
Anaemia		0 2 (15.4%)

DISCUSSION

There was no significant difference in age ($P=0.952$) among studied groups, no significant difference in disease duration ($P=0.126$). Disease activity at entry was higher in the CYC group (16 ± 2.9) than for the rituximab group (12 ± 2.8), ($P=0.001$). In this study, CYC was more effective than rituximab in inducing clinical response at three months, ($P=0.003$), this difference was maintained at six months, ($P=0.001$) and, at nine months, ($P=0.004$). Rituximab achieved only a 50% reduction in SLEDAI score. This finding goes with the results of the Merrill JT et al. (EXPLORER trial)[28] which showed no difference between rituximab and placebo at week 52 in achieving major clinical response or partial clinical response. While on the other hand, this study's finding disagreed with Gabriella Moroni et al. [29] which showed that rituximab was equal to CYC in reducing SLEDAI score at three months and 12 months from baseline without significant difference between them. Tanaka et al. [30] also had demonstrated that rituximab had achieved major clinical response and partial clinical response in (64.3%) of patients at week 28, these results are different possibly because Tanaka et al. enrolled only small sample (only 14 patients with heterogeneous manifestation, five patients had central nervous system involvement and only six patients had marked renal involvement).t three months from baseline for rituximab group (26.9%) of patients achieved CRR or IRR, and (73.1%) were non-responders, while for CYC group, (53.9%) achieved CRR or IRR, and (46.2%) were non-responders, the difference was not statistically significant ($P=0.069$). Rituximab was not effective to induce renal remission at three months. Gabriella Moroni et al. [29=30] had found that after three months, the renal response achieved in both rituximab and CYC arm without significant difference. At six months, for rituximab group (50%) achieve CRR or IRR and (50%) were non-responders, while for CYC group (76.9%) achieve CRR or IRR and (23.1%) were non-responders, the difference was not statistically significant (P -value=0.107). Candido Diaz-Lagares et al. [31] found that rituximab effectively achieved renal response (complete and partial) at six months. At nine months, CRR or IRR rate was (50%) for rituximab and (84.6%) for CYC, non-responder or relapse for rituximab (50%) and (15.4%) for CYC. CYC was more effective than rituximab in achieving CRR and IRR at nine months ($P= 0.036$). Gabriella Moroni et al. found that all patients in rituximab arm developed renal response at one year. These concordant results attributed to the difference in sample selection, for example, the disease duration was longer in the rituximab arm than in the CYC arm, along with, patients who received rituximab were older and had an adverse finding on renal biopsy (in term of higher chronicity and activity index) than those treated with CYC.

Patients who received rituximab treated with multiple CYC and MMF courses before assignment to rituximab arm, so this response can be attributed to the effect of previous immune suppressive therapy or implies that rituximab is more effective only in long-standing refractory SLE and LN. Candido Diaz-Lagares et al. found that rituximab effectively achieved renal response (complete and partial) at 12 months. In Candido Diaz-Lagares et al., (50%) of patients had the refractory disease and (80%) had received CYC therapy during their illness. Another observational study, the Artim-Esen et al., Istanbul University, Turkey [32] found that rituximab had achieved complete renal response in class IV LN, but still in long-standing refractory disease. This study's finding parallels with the finding of Rovin et al. (LUNAR trial) [33], which demonstrate that at 52 weeks, rituximab failed to achieved CRR or PRR compared to placebo. Safety: no new safety issue immersed from this study regarding the use of rituximab, most of rituximab side effects were infusion related reaction (42.3%) which is comparable to the rate of infusion reaction in Merrill JT et al. (EXPLORER trail)[28] of (43.8%). In this study only (7.6%) of patients develop serious side effects. For CYC group the rate of side effects was (46.2%), which was comparable to the rate of side effects recorded in Gabriella Moroni et al. [29]

CONCLUSIONS

Cyclophosphamide is more effective than rituximab in inducing remission in patients with Lupus nephritis. Extending this study with a longer duration of follow up is needed to clarify the exact role of rituximab in treating Lupus nephritis. Measurement of CD-20 is needed to assess its relation with the renal response. Rituximab may still have a role in the treatment of a patient with refractory and long-standing SLE.

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