

# Efficacy and Safety of Rituximab Therapy for Lupus Nephritis Among SLE Female Patients; a Retrospective Hospital-Based Study

Khansa Osama Abdelkarim Aloub<sup>1</sup>, Noha Ibrahim Ahmed Eltahirm<sup>1,2</sup>, Elnour Mohammed Elagib<sup>1,2</sup>, Mohammed Elmujtba Adam Essa<sup>3,4</sup>, Mustafa Mohammed Ali Hussein<sup>3,4</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Omdurman Military Hospital, Omdurman, Sudan; <sup>2</sup>Department of Medicine, Faculty of Medicine, Karary University, Omdurman, Sudan; <sup>3</sup>Department of Clinical Medicine, Medical and Cancer Research Institute, Nyala, Sudan; <sup>4</sup>Faculty of Medicine, Al fashir University, Al Fashir, Sudan

Correspondence: Mohammed Elmujtba Adam Essa, Department of Clinical Medicine, Medical and Cancer Research Institute, Nyala, Sudan, Tel +24990700938, Email Awadali818@yahoo.com

**Background:** Renal affection in systemic lupus erythematosus (SLE) is a high-risk manifestation in which novel treatment strategies are required, particularly in patients who show lower response to conventional therapy. Rituximab has been used as an off-label treatment for lupus nephritis (LN) for the last ten years. This study aims to assess the outcome of the use of rituximab to treat LN patients.

**Methods:** A retrospective cross-sectional study included 40 LN patients on Rituximab therapy who attended the Rheumatology clinic at Omdurman Military Hospital, Khartoum, Sudan. Between January to July 2020. Data were collected from the hospital records and included demographic, duration of disease and Rituximab doses. Renal biopsy, renal function parameters, albumin-creatinine ratio, hematological parameters and inflammatory markers. Assessment of the outcomes was conducted by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI score). Data were analyzed by using Statistical Package for Social Studies Program (SPSS, V. 21.0. IBM; Chicago). Chi-square test was used as significance test, the P. value was considered as significant at level 0.05 and akk continues variables had a normal distribution with Kolmogorov–Smirnov test.

**Results:** Renal function test showed significant improvement after 6 months of treatment with Rituximab. In addition, the mean of the SLE Activity Index 2000 (SLEDAI 2K) was significantly decreased with remarkable improvement in the histological degree of LN. The histology of renal biopsy of the patients commonly was diffuse proliferative nephritis followed by minimal mesangial glomerulonephritis, mesangial proliferative LN then membranous nephritis respectively. Improvement was common among the patients aged 20–39 years, those with disease duration less than 5 years, who received 4 doses and rituximab as the initial modality.

**Conclusion:** Rituximab therapy is effectively managing patients with lupus nephritis, after 6 months of follow-up, Patients showed remarkable clinical and laboratory improvement.

**Keywords:** rituximab, LN, SLE, conventional therapy

## Introduction

SLE is a chronic multisystem autoimmune disease that is highly heterogeneous in its presentation. It causes various symptoms and signs, which makes it a challenging condition for clinical diagnosis and treatment, affecting both female-to-males with a ratio of 8–9:1.<sup>1,2</sup> New insight into immunopathogenesis provides theories for developing potential clinical biomarkers and therapeutic targets of SLE.<sup>3</sup> One of its most severe manifestations is lupus nephritis (LN) which is associated with increased morbidity and mortality.<sup>4</sup>

Different pathophysiological mechanisms have been involved in the development of LN in SLE patients.<sup>5</sup> A combination of genetic, environmental and immunological factors mediates the processes that result in renal damage.<sup>6</sup> Of special importance for the present review is the role of the B cells, which are hyperactive in SLE. The



B cells mediate and regulate antibody production, interact with memory T cells and stimulate pro-inflammatory cytokine production, all of which make them essential components of the pathophysiology of LN.<sup>7</sup> It is for these reasons that the use of rituximab is proposed. This monoclonal antibody is directed against CD20, an antigen expressed on the surface of mature and immature B cells. CD20 regulates the initiation of the cell cycle. The binding of the antibody to Fc receptor induces apoptosis and cytotoxicity, mediated by both complement and antibodies.<sup>8</sup> LN is an immune complex glomerular nephritis that progresses as a result of recurrent complications of SLE.<sup>9</sup> The pathophysiology of LN involves a variety of pathogenic mechanisms which are intrarenal and extrarenal pathogenic mechanisms.<sup>10</sup> The extrarenal factors include complex combinations of genetic variants that are changed in each patient; this may clarify the variability of clinical manifestations.<sup>5</sup>

The use of biologic therapies as an adjunct to disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of autoimmune and rheumatologic diseases is rapidly expanding, owing to the good efficacy and safety profiles of these drugs, and the better understanding of the initial targets of altered immune regulation and activity in various diseases.<sup>11</sup> Although some of the biological therapies have been found to be useful in more than one disease, others are specific to a single disease. Research is ongoing to identify other molecular targets.<sup>12</sup>

The development of biological therapies has had an impact on the management of several medical conditions.<sup>13</sup> Their use in systemic lupus erythematosus (SLE), however, remains very limited.<sup>14</sup> The aim of the study is to assess the outcome of the use of rituximab to treat SLE patients with lupus nephritis.

## Materials and Methods

### Study Design

This is an analytical retrospective cross-sectional hospital-based study.

### Study Area

The study was conducted at the department of rheumatology, Omdurman Military Hospital in Khartoum state, Sudan.

### Study Population

SLE patients with LN attended the rheumatologic department of Omdurman Military Hospital and received Rituximab.

### Sample Size Determination

Total coverage of all SLE patients with lupus Nephritis on Rituximab treatment during the study period is 40 patients who are treated at the department of rheumatology, Omdurman Military Hospital in Khartoum state, Sudan.

### Data Collection Tools and Methods

Data collection is carried out by the principal investigator. After recruiting the study subjects, structured questionnaires will be used to collect data composed of; demographic, duration of the SLE and Rituximab doses (using Patients Hospital Records), and all the patients were treated according to the standard protocol treatment of SLE patients with LN (received 500 mg once/week for 1 month). Hematological parameters (hemoglobin, leucocyte and platelet counts) and inflammatory markers (ESR, CRP, C3 and C4) were compared at admission and after 6 months. Assessment of the outcomes was being measured through the parameters of renal function test (urea, creatinine, albumin-creatinine ratio) and urine dipstick (for proteinuria) in addition to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI score). Screening for tuberculosis, hepatitis and HIV was performed on all the patients before treatment with rituximab as most of the patients were been treated by MMF or CNI but they have not shown any improvement, so we shifted to rituximab. Regarding the adverse side effect of rituximab no patients report any side effect during the follow up of the treatment.

### Study Variables

Independent variables (Socio-demographic characteristics of participants, age, gender, duration of disease, number of Rituximab doses of Hematological parameters (hemoglobin, leucocyte and platelet counts), renal function (urea,

creatinine, albumin-creatinine ratio) and proteinuria), inflammatory markers (ESR, CRP, C3 and C4), dependent variables (Rituximab outcome by SLEDAI-2K Score for SLE patients).

## Data Analysis

Data were analyzed by using Statistical Package for Social Studies Program (SPSS, V. 21.0. IBM; Chicago). Chi-square test was used as significance test, P value was considered as significant at level 0.05 and akk continues variables had a normal distribution with Kolmogorov–Smirnov test.

## Ethical Consideration

Ethical approval was obtained from Sudan medical specialization board (SMSB). Written informed consent was obtained from patients.

## Results

The mean SLE Activity Index 2000 (SLEDAI 2K) was significantly decreased after 6 months of rituximab use ( $34.5 \pm 13.7$  vs  $12.3 \pm 16.1$ ; P. value = 0.000) with mean difference =  $-22.2$  (Figure 1). In addition to improvement (complete and partial) presented in 36 (90%) patients, deterioration in 2 (5%) and not responding in 2 (5%) patients. Improvement was common among the patients aged 20–39 years more than others (P. value = 0.000) and also higher among those with disease duration less than 5 years more than others (P. value = 0.01). The mean disease duration was found to be  $5.8 \pm 4$  years and one-half (n = 20; 50%) had a duration of fewer than 5 years (Table 1).

The patients who received 4 doses and rituximab as initial modality shows better response than others (P. value = 0.036) (Figure 2), the number of Rituximab doses was less than 4 doses in 6 (15%) patients, 4 doses in 20 (50%) and more than 4 doses in 14 (35%) patients (Table 1).

In general, the study included a total of 40 female SLE patients with LN on Rituximab treatment, their mean age was  $34.9 \pm 8$  years and the majority of them 16 (40%) belonged to the age group from 30 to 39 years (Table 1). The hematological parameter of the study group showed that there was a significant rising in hemoglobin ( $9.9 \pm 2.7$  vs;  $11.4 \pm 1.6$  P. value = 0.000) and platelets count ( $220.5 \pm 143.4$  vs  $265 \pm 103$ ; P. value = 0.001) after 6 months of Rituximab use.

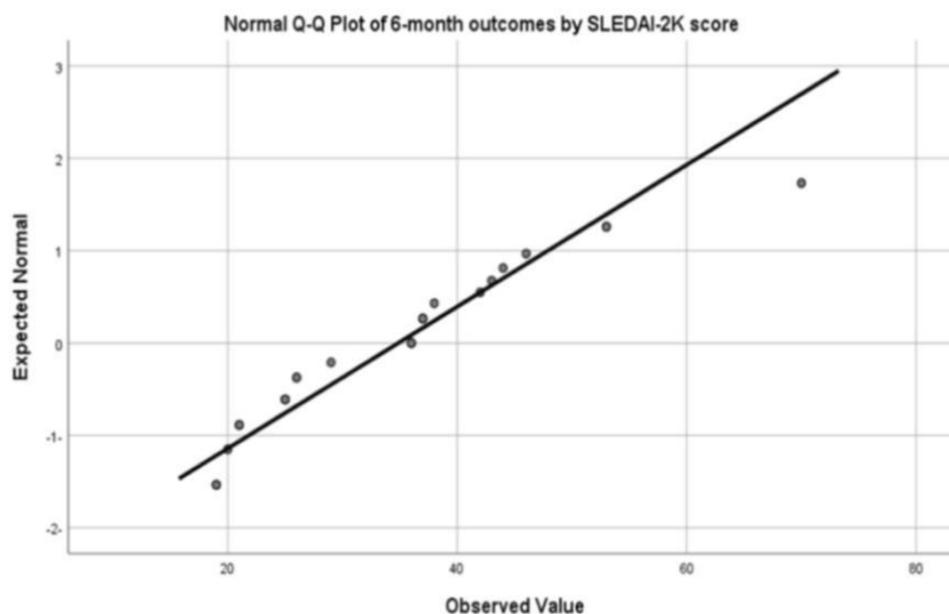


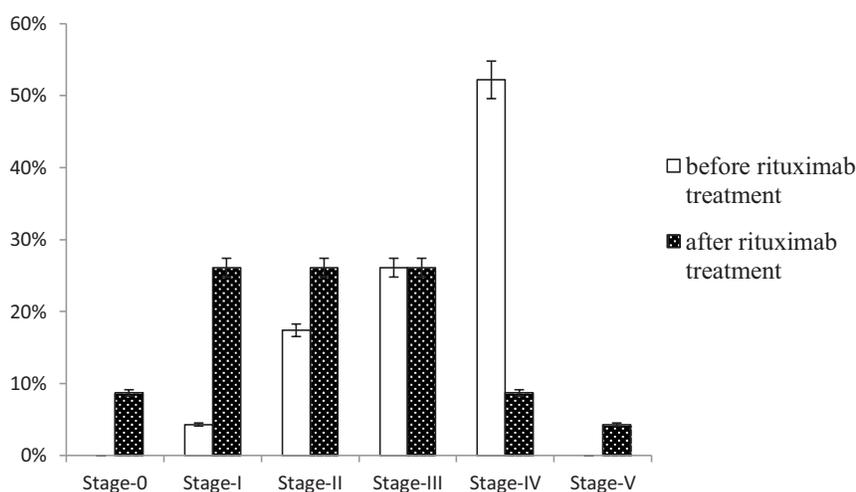
Figure 1 Shows the distribution Q-Q of 6 months outcome by SLEDAI-2K score.

**Table 1** Shows the Age Distributions, Number of Rituximab Doses and the Disease Duration of SLE Patients with Lupus Nephritis on Rituximab Treatment (N = 40)

Duration of Disease (Yrs); M±SD	% of the Patients
Less than 5 years	50
From 5–10 years	40
More than 10 years	10
<b>Age by years</b>	<b>%</b>
Less than 20	10
20–29	37.5
30–39	40
More than 40	12.5
<b>Number of doses</b>	<b>%</b>
Less than 4	15
4	50
More than 4	35

In inflammatory investigations, CRP ( $13.4 \pm 7.5$  vs  $2.1 \pm 1.7$ ; P. value = 0.000) and ESR ( $72.3 \pm 35$  vs  $39.3 \pm 4.5$ ; P. value = 0.000) were significantly decreased after 6 months of Rituximab use. Also, the levels of C3 levels (40% vs 75%; P. value = 0.002) and C4 levels (74.5% vs 80%; P. value = 0.000) were significantly increased after 6 months of Rituximab use (Figure 1).

In the renal function test, there was significant improvement in urea levels ( $72.6 \pm 50.9$  vs  $49.4 \pm 29.8$ ; P. value = 0.000), creatinine levels ( $3.4 \pm 2.5$  vs  $1.8 \pm 0.4$ ; P. value = 0.000) and albumin creatinine ratio (477.5 vs 185; P. value = 0.000) after 6 months of Rituximab use. In addition, 3(7.5%) patients had proteinuria of 1+ or less before Rituximab use and 29 (72.5%) after Rituximab use (P. value = 0.000). Among the patients who underwent renal biopsy (n = 23). Only 4.3% of patients showed minimal mesangial glomerulonephritis before the use of rituximab and raise it to 34.8% after it was been used. Before the use of rituximab, only 17.4% of the patients' renal biopsy showed mesangial proliferative LN, the percentage increased to 26.1% after 6 months receiving of rituximab, 26.1% of the patients showed focal proliferative



**Figure 2** Shows the scores of SLE Disease Activity Index 2000 (SLEDAI 2K) before and after Rituximab treatment (N=40).

nephritis before and after rituximab treatment, 52.2% of all the patients showed diffuse proliferative nephritis which decreased to 8.7% after 6 months treatment with rituximab and only 1% after treatment showed membranous nephritis. Non affordability was the main cause of not renal biopsy conduction in 10 out of 17 patients (58.8%), patient refusal in 6/17 (35.3%), and non-availability in 1/17 (5.9%) patients.

## Discussion

The prognosis of SLE and LN patients has improved over the last half-century due to the use of steroids and other agents as well as the introduction of renal dialysis and transplant.<sup>15</sup> Still, the damaging effect occurring by corticosteroid treatment increased the rate of morbidity among these patients.<sup>16</sup> It is important to initiate induction treatment with the best possible clinical efficacy at a very early stage of LN. The principal goals of LN management are renal remission with minimal toxic effects.<sup>17</sup> As a result, efforts and studies have been focused on alternatives that can induce and maintain disease remission and improve overall outcomes.<sup>18</sup> Therefore, in this study, we are evaluating the outcome of Rituximab (RTX) to treat patients with LN among SLE Patients.

The mean age of our study participants is 34.9±8 years and the majority of them 40% belonged to the age group of 30–39 years. These findings were comparable to others where it concluded the mean age is 36.2 years,<sup>19</sup> and other studies reported mean ages of 30 and 31 years.<sup>20</sup>

In regards to the renal function test, there was a significant improvement in urea levels (72.6±50.9 vs 49.4±29.8; P. value = 0.000), creatinine levels (3.4±2.5 vs 1.8±0.4. P. value = 0.000). These findings are in agreement with published studies where it found a significant reduction in creatinine levels after 6 months of administration of Rituximab.<sup>20,21</sup> Regarding the hematological parameters, there was a significant improvement in hemoglobin (9.9±2.7 vs 11.4±1.6; P. value = 0.000) and platelet count (220.5±143.4 vs 265±103; P. value = 0.001) after six months of Rituximab use. Similar findings were reported by some authors who studied the effects of RTX in refractory autoimmune hemolytic anemia.<sup>22</sup>

The albumin creatinine ratio in this study was statistically decreased after 6 months of Rituximab use, leading to reducing of the median urinary protein creatinine ratio from 446 to 190 mg/mmol. Other studies showed similar findings (80). The ultimate aim of LN management is to prevent nephron loss and, thus, chronic kidney diseases, particularly end-stage kidney disease (ESKD), so conventicle therapy such as immunosuppressants is used.<sup>23</sup> However, many patients do not achieve short-term remission and experience CKD with these regimens as a result of a new treatment paradigm, by switching to a combination such as rituximab and anti-CD20 obinutuzumab showed very satisfying results.<sup>24,25</sup> The levels of CRP, ESR, C3 and C4 levels were significantly increased after 6 months of Rituximab use. The same coordination was reported.<sup>26</sup>

Only 4.3% of patients showed minimal mesangial glomerulonephritis before the use of rituximab and raise it to 34.8% after it was been used. Before the use of rituximab, only 17.4% of the patients' renal biopsy showed mesangial proliferative LN, the percentage increased to 26.1% after 6 months receiving of rituximab, 26.1% of the patients showed focal proliferative nephritis before and after rituximab treatment, 52.2% of all the patients showed diffuse proliferative nephritis which decreased to 8.7% after 6 months treatment with rituximab and only 1% after treatment showed membranous nephritis.

A remarkable improvement in the histological degree of lupus nephritis was detected by renal biopsy, as the frequency of stage-0 and stage-I (minimal mesangial glomerulonephritis) were 4.3% (n = 1) before Rituximab use and raise to 34.8% (n = 8) after Rituximab use. Stages II–V (mesangial proliferative LN, focal proliferative nephritis and diffuse proliferative nephritis) were found in 95.6% of patients before Rituximab use compared to 65.2% after follow-up (Figure 2). These results were consistent with a review that showed renal activity index (AI) was determined by morphologic alteration in renal biopsy, and the maximum score is 24 points. These trials mostly included patients with active LN despite treatment, WHO or International Society of Nephrology/Renal Pathology Association class III (eight patients), IV (33 patients), III–V (one patient), IV–V (seven patients).<sup>27</sup> Twelve patients had class V LN. In all patients, there was a significant reduction in AI following RTX treatment (mean difference = -3.46; 95% CI: -4.43 to -2.50, P < 0.01).<sup>18,28</sup>

Treatment with rituximab has produced a variety of serologic and clinical side effects depending on the disease; in SLE some studies reported resistant clinical manifestations, such as renal, CNS, hematological features and vasculitic.<sup>29</sup> Fortunately, none of these effects were been reported in our study patients during the duration of follow up.

Finally, our study showed that, improvement was common among patients aged from 20 to 29 years (P. value = 0.004), patients with diseases duration <5 years (P. value = 0.001), patients were taking 4 doses of Rituximab (P. value = 0.036) and patients were taking Rituximab as initial modality (P. value = 0.045).

Limitation of the study: all the patients were proposed to do renal biopsy; however, only 57.5% of them performed while the rest either refused to go through the procedure or were financially unoffered.

In conclusion, Rituximab treatment in patients with LN showed effective results based on SLEDAI 2K score. There was a significant rise in hemoglobin and platelet count in hematological parameters, reduce urea, creatinine, ACR as well as proteinuria in renal function parameters and reduce CRP, ESR and normalized C3/C4 in inflammatory markers, also it gave a transition into favourable degrees of lupus nephritis. Moreover, the improvement was significant in the patients aged 20–29 years.

## Abbreviations

ACR, American College Of Rheumatology; ADCC, Antibody Dependent Cellular Cytotoxicity; AEs, Adverse Events; ANA, Antinuclear Antibodies; ANA, Antineutrophil Cytoplasmic Antibody; APC, Antigen-Presenting Cell; BCR, B Cell Receptor; BLYS, B-Lymphocyte Stimulator; CKD, Chronic Kidney Disease; CMC, Complement Mediated Cytotoxicity; CNS, Central Nervous System; CR, Complete Remission; CYC, Cyclophosphamide; DHEA, Dehydroepiandrosterone; DIL, Drug-Induced Lupus; DLE, Discoid Lupus Erythematosus; DMARDs, Disease-Modifying Anti-Rheumatic Drugs; EBV, Epstein-Barr Virus; ESRD, End Stage Renal Disease; EXPLORER, Randomised, Double-Blind, Placebo-Controlled Exploratory Phase II/III SLE Evaluation Of Rituximab; HACA, Human Antichimeric Antibodies; HCQ, Hydroxychloroquines; IL, Interleukin; ISN/RPS, International Society Of Nephrology/Renal Pathology Society; LILRB4, Leukocyte Immunoglobulin Like Receptor B4; LN, Lupus Nephritis; LUNAR, Lupus Nephritis Assessment with Rituximab; MHC, Major Histocompatibility Complex; MMF, Mycophenolate Mofetil; MTX, Methotrexate; NET, Neutrophil Extracellular Traps; NLE, Neonatal Lupus Erythematosus; NSAID, Non-Steroid Anti-Inflammatory Drug; PR, Partial Remission; RA, Rheumatoid Arthritis; RANTES, Regulated Upon Activation, Normal T Cell Expressed And Presumably Secreted; SLEDAI, SLE Disease Activity Index; SRI, SLE Responder Index; TNF, Tumor Necrosis Factor; WHO, World Health Organization.

## Data Sharing Statement

All the data used in the study are available from the first and corresponding author on reasonable request.

## Ethics Approval for the Study

Obtained from federal Ministry of health Sudan and Sudan medical specializations board.

## Consent for Publication

Obtained.

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## Author Contributions

All authors made a significant contribution to this work, whether that is in the study design, acquisition of data, conception, execution, data analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

All authors declare that they have no conflict of interest and the study complies with the Declaration of Helsinki with no received fund.

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