

Initial Preserved Renal Function as a Predictor of Favorable Renal Response to Rituximab in Refractory or Relapsing Lupus Nephritis: A Single-center Cohort Study in Korea

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Objective. Previous studies investigating the beneficial effect of rituximab on lupus nephritis (LN) reported controversial results. There have been few reports of renal response to rituximab according to renal function. We investigated the efficacy of rituximab in refractory/relapsing LN and the role of renal function as a predictor of renal response. **Methods.** From 2016 to 2019, we retrospectively reviewed 22 patients with refractory/relapsing LN receiving rituximab. Renal responses (complete and partial) at 6 and 12 months were compared between normal (glomerular filtration rate [GFR] ≥ 90 mL/min/1.73 m², n = 11) and decreased (GFR < 90 mL/min/1.73 m², n = 11) GFR groups. Multivariate Cox regression analysis was used to assess predictors of renal response. **Results.** At baseline, the decreased GFR group had a higher urine proteinuria to creatinine ratio (p = 0.008) and proportion of refractory LN (p = 0.010) and previous cyclophosphamide therapy (p = 0.035) than the normal GFR group. The overall renal response rate was 45.5% (10 patients) at 6 months and 54.5% (12 patients) at 12 months. Renal response rates were higher in the normal GFR group (81.8% and 90.9% at 6 and 12 months, respectively) than in the decreased GFR group (9.1% and 18.2% at 6 and 12 months, respectively; p < 0.001). Normal GFR and anti-La were associated with renal response to rituximab, with hazard ratios of 9.256 (p = 0.008) and 5.478 (p = 0.041), respectively. **Conclusion.** Rituximab is an effective therapy for refractory/relapsing LN, particularly in patients with preserved renal function. (*J Rheum Dis* 2022;29:22-32)

Key Words. Lupus nephritis, Systemic lupus erythematosus, Kidney, Rituximab, Glomerular filtration rate

INTRODUCTION

Lupus nephritis (LN) is a major organ involvement complication of systemic lupus erythematosus (SLE) and occurs in up to 60% of patients with SLE. The current treatment regimen for LN is a combination of corticosteroids and immunosuppressants, including cyclophosphamide (CYC), mycophenolate mofetil (MMF), and tacrolimus. However, only 50% ~ 70% of patients achieve remission, whereas the rest do not achieve remission or experience a relapse [1,2]. Eventually, 10% to 30% of patients progress to end-stage renal disease (ESRD). These poor outcomes of LN warrant new therapeutic agents, but to date,

there is no standard treatment for refractory or relapsing LN.

B cells play crucial roles in the pathogenesis of SLE through autoantibody production, presentation of autoantigens to T cells, and cytokine production [3]. Rituximab is a chimeric monoclonal CD20 antibody that is effective in rheumatoid arthritis and antineutrophil cytoplasmic antibody-associated vasculitis [4,5]. However, the effects of rituximab on SLE are debated, and further research is required [6-9]. Discrepancies between randomized controlled trials and other observational studies require us to focus on the factors associated with renal response to rituximab. Several prognostic factors for LN have been

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studied, including proteinuria, renal function, serologic markers, and pathological class [10,11]. However, few studies have reported the efficacy of rituximab in LN according to renal function. Therefore, the aim of the present study was to evaluate the effectiveness of rituximab in refractory or relapsing LN and determine whether or not renal function is useful in predicting renal response to rituximab.

MATERIALS AND METHODS

Study population

We enrolled 22 adult patients with refractory or relapsing LN who had been started on rituximab from January 2016 to December 2019 at a tertiary referral hospital in South Korea. They were diagnosed with LN according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification [12]. Refractory LN was defined as an inadequate renal response after standard immunosuppressive therapy including CYC and MMF. Patients were followed-up for 12 months after rituximab therapy. Those with renal replacement treatment were excluded. This study was conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Review Board of the Asan Medical Center approved this study (IRB number: 2020-0184) and waived the requirement for informed consent because of the retrospective study design.

Data collection

We retrospectively reviewed the electronic medical records of patients for age, sex, SLE and LN durations, medications, and the SLE Disease Activity Index-2K (SLEDAI-2K) score. We collected laboratory data, including the serum creatinine level, glomerular filtration rate (GFR), urine protein to creatinine ratio (UPCR), presence/absence of hematuria, serum albumin level, complement level, and anti-double-stranded DNA antibody (anti-dsDNA) level. Renal pathology was reviewed to measure the activity and chronicity indexes. We estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation. Sequential serological and urinary data were also documented at 3, 6, and 12 months. Patients were classified into two groups according to GFR at the start of rituximab therapy: normal ($\text{GFR} \geq 90 \text{ mL/min/1.73 m}^2$) and decreased ($\text{GFR} < 90 \text{ mL/min/1.73 m}^2$) GFR groups.

Renal outcome

Renal response was defined as the achievement of complete or partial renal response. Complete renal response (CR) was defined as a $\text{UPCR} < 500 \text{ mg/g}$ and normal or stable GFR (within 10% change in GFR if previously abnormal) [13,14]. Partial renal response (PR) was defined as a $\geq 50\%$ reduction of UPCR to subnephrotic levels and normal or stable GFR. The responder was defined as a patient who achieved a renal response. Relapse was defined as reproducible doubling of UPCR to $> 1,000 \text{ mg/g}$ after CR or to $> 2,000 \text{ mg/g}$ after PR [15]. Changes in clinical parameters from baseline to 3, 6, and 12 months were also evaluated.

Statistical analysis

Continuous variables are expressed as median (interquartile range [IQR]). They were compared using the Mann-Whitney U-test. Categorical data are expressed as number (percentage). They were analyzed using the chi-squared test and Fisher's exact test. Wilcoxon signed-rank test was used to compare paired clinical parameters within the two groups at different time points. We performed Kaplan-Meier analysis with the log-rank test to assess the cumulative renal response rates. Univariate and multivariate Cox proportional hazard analyses with a stepwise method were conducted to calculate the hazard ratio (HR) and 95% confidence interval (CI) for renal response to rituximab. Variables with a $p\text{-value} < 0.2$ in the univariate Cox analysis were included in the multivariate Cox analysis. A $p\text{-value} < 0.05$ was considered to be statistically significant in other analyses.

RESULTS

Baseline characteristics and treatment regimen in normal and decreased GFR groups

We enrolled a total of 22 patients with LN, including 2 (9.1%) male and 20 (90.9%) female, with a median age of 39 (IQR, 24 ~ 50) years. The median SLE and LN durations were 10.7 (IQR, 6.4 ~ 17.8) and 5.8 (IQR, 3.2 ~ 8.6) years, respectively. The ISN/RPS classification was class III in 11 (50%) patients, class IV in 10 (45.5%) patients, and pure class V in one (4.5%) patient. In 19 patients with the activity and chronicity indexes, the median scores were 6 (IQR, 5 ~ 10) and 3 (IQR, 1 ~ 4), respectively. Ten cases were refractory, whereas the others were relapsing. Eleven patients showed normal GFR levels at the start of rituximab therapy, whereas the remaining 11 patients

Table 1. Baseline characteristics of patients in normal and decreased glomerular filtration rate groups

Variable	Normal GFR (n = 11)	Decreased GFR (n = 11)	p-value
Age (yr)	31 (24 ~ 49)	43 (24 ~ 56)	0.300
Female	10 (90.9)	10 (90.9)	1.000
Duration since SLE diagnosis (yr)	12.4 (3.2 ~ 18.3)	8.7 (6.8 ~ 15.4)	1.000
Duration since LN diagnosis (yr)	5.7 (2.4 ~ 8.1)	5.8 (4.2 ~ 10.1)	0.519
Duration since last kidney biopsy (yr)	2.7 (1.0 ~ 6.4)	5.8 (3.3 ~ 10.1)	0.116
ISN/RPS classification			
Class III	6 (54.5)	5 (45.5)	0.670
Class IV	4 (36.4)	6 (54.5)	0.392
Pure class V	1 (9.1)	0 (0)	1.000
Class III/IV	1 (9.1)	2 (18.2)	1.000
Class IV/V	0 (0)	2 (18.2)	0.476
Activity index	6 (3 ~ 9)	8 (5 ~ 11)*	0.492
Chronicity index	2 (1 ~ 4)	4 (2 ~ 5)*	0.310
Refractory LN	2 (18.2)	8 (72.7)	0.010
Previous immunosuppressants			
Cyclophosphamide	6 (54.5)	11 (100)	0.035
Mycophenolate mofetil	11 (100)	10 (90.9)	1.000
Azathioprine	7 (63.6)	7 (63.6)	1.000
Tacrolimus	9 (81.8)	11 (100)	0.476
Hydroxychloroquine	11 (100)	11 (100)	N/A
Immunosuppressants before the start of rituximab			
Cyclophosphamide	0 (0)	4 (36.4)	0.090
Mycophenolate mofetil	8 (72.7)	4 (36.4)	0.087
Azathioprine	1 (9.1)	0 (0)	1.000
Tacrolimus	7 (63.6)	3 (27.3)	0.087
Hydroxychloroquine	11 (100)	7 (63.6)	0.090
Glucocorticoid treatment	8 (72.7)	8 (72.7)	1.000
Prednisolone dose (mg/day)	5.0 (0 ~ 20.0)	7.5 (0 ~ 20.0)	0.949
Rituximab regimen			
1,000 mg × 2 infusions	10 (90.9)	6 (54.5)	0.149
500 mg × 4 infusions	1 (9.1)	3 (27.3)	0.586
500 mg × 3 infusions	0 (0)	1 (9.1)	1.000
500 mg × 2 infusions	0 (0)	1 (9.1)	1.000
Laboratory finding			
Serum creatinine (mg/dL)	0.70 (0.48 ~ 0.75)	1.59 (0.97 ~ 2.15)	<0.001
GFR (mL/min/1.73 m ²)	116 (101 ~ 123)	39 (27 ~ 79)	<0.001
UPCR (mg/g)	1,275 (920 ~ 2,199)	3,110 (2,264 ~ 5,682)	0.008
UPCR < 1,000 mg/g	4 (36.4)	0 (0)	0.090
UPCR ≥ 3,000 mg/g	2 (18.2)	7 (63.6)	0.080
Microscopic hematuria	5 (45.5)	4 (36.4)	1.000
Serum albumin (g/dL)	3.1 (2.8 ~ 3.4)	3.2 (1.9 ~ 3.6)	0.748
C3 (mg/dL)	52.1 (41.9 ~ 90.7)	76.2 (38.7 ~ 109.0)	0.438
C4 (mg/dL)	9.8 (4.5 ~ 15.1)	22.1 (14.6 ~ 25.2)	0.007
Anti-dsDNA titer (IU/mL)	47.7 (7.2 ~ 488.0)	11.9 (3.5 ~ 33.8)	0.401
Anti-ENA positivity			
Anti-Ro	7/10 (70)	5/11 (45.5)	0.387
Anti-RNP	6/10 (60)	4/11 (36.4)	0.395
Anti-Sm	4/10 (40)	4/11 (36.4)	1.000
Anti-La	2/10 (20)	1/11 (9.1)	0.586
SLEDAI-2K score	12 (6 ~ 16)	8 (6 ~ 16)	0.606

Data are expressed as median (interquartile range) or number (%). GFR: glomerular filtration rate, SLE: systemic lupus erythematosus, LN: lupus nephritis, ISN/RPS: International Society of Nephrology/Renal Pathology Society, UPCR: urine protein to creatinine ratio, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, N/A: not available. *Three patients were excluded because of missing data.

had decreased GFR levels. Among them, 8 patients had GFR < 60 mL/min/1.73 m² at baseline.

We compared the baseline characteristics of patients between normal and decreased GFR groups (Table 1). The decreased GFR group showed higher proportions of refractory LN (72.7% vs. 18.2%, $p=0.010$) and previous CYC therapy (100% vs. 54.5%, $p=0.035$) than the normal GFR group. At the start of rituximab therapy, the median serum creatinine level was 0.70 (IQR, 0.48~0.75) mg/dL in the normal GFR group and 1.59 (IQR, 0.97~2.15) mg/dL in the decreased GFR group; the median GFR level was 116 (IQR, 101~123) mL/min/1.73 m² in the normal GFR group and 39 (IQR, 27~79) mL/min/1.73 m² in the decreased GFR group. The median UPCr level was higher in the decreased GFR group than in the normal GFR group (3,110 [IQR, 2,264~5,682] mg/g vs. 1,275 [IQR, 920~2,199] mg/g, $p=0.008$). There was no significant difference between the two groups in the proportion of patients with UPCr < 1,000 or $\geq 3,000$ mg/g. The minimum UPCr level was 896 mg/g in the entire study population. The median C4 level was lower in the normal GFR group than in the decreased GFR group (9.8 [IQR, 4.5~15.1] mg/dL vs. 22.1 [IQR, 14.6~25.2] mg/dL, $p=0.007$). Other laboratory findings, including anti-dsDNA titers, anti-ENA positivity, or the SLEDAI-2K score, did not differ between the groups.

Table 2 shows concomitant treatment with rituximab therapy. MMF was used in 54.5% of patients during 0~6

months and 63.6% of patients during 6~12 months. Both groups received almost similar treatments during the follow-up. For 6~12 months, tacrolimus was used more in the normal GFR group than in the decreased GFR group (81.8% vs. 27.3%, $p=0.030$). Rituximab was re-administrated during 6~12 months to one patient in the normal GFR group and one patient in the decreased GFR group.

Renal response to rituximab in normal and decreased GFR groups

The overall renal response was achieved in 10 patients (CR, eight patients; PR, two patients) at 6 months and 12 patients (all CR) at 12 months. When comparing the treatment regimens of responders (12 patients) and non-responders (10 patients) up to the date of response or last follow-up, there was no difference in the median cumulative dose of rituximab (2,000 [IQR, 2,000~2,000] mg vs. 2,000 [IQR, 1,875~2,000] mg, $p=0.456$) and prednisolone (8.2 [5.0~18.0] mg/day vs. 6.4 [0.8~12.7] mg/day, $p=0.539$). The proportion of patients who had ever been treated with prednisolone ≥ 30 mg/day did not differ between the two groups (responder vs. non-responder, 25.0% vs. 30.0%, $p=1.000$). The proportion of patients with concomitant treatment including CYC (8.3% vs. 10.0%, $p=1.000$), MMF (50.0% vs. 60.0%, $p=0.691$), azathioprine (8.3% vs. 0%, $p=1.000$), tacrolimus (58.3% vs. 50.0%, $p=1.000$), and hydroxychloroquine

Table 2. Concomitant treatment after rituximab therapy in normal and decreased glomerular filtration rate groups

Variable	Normal GFR (n = 11)	Decreased GFR (n = 11)	p-value
0~6 months			
Cyclophosphamide	1 (9.1)	0 (0)	1.000
Mycophenolate mofetil	8 (72.7)	4 (36.4)	0.087
Azathioprine	1 (9.1)	1 (9.1)	1.000
Tacrolimus	8 (72.7)	4 (36.4)	0.087
Hydroxychloroquine	11 (100)	8 (72.7)	0.214
Glucocorticoid	9 (81.8)	8 (72.7)	1.000
Prednisolone dose (mg/day)	7.9 (0.4~12.7)	6.2 (0~12.4)	0.606
Re-infusion of rituximab	0 (0)	0 (0)	N/A
6~12 months			
Cyclophosphamide	0 (0)	1 (9.1)	1.000
Mycophenolate mofetil	9 (81.8)	5 (45.5)	0.183
Azathioprine	1 (9.1)	1 (9.1)	1.000
Tacrolimus	9 (81.8)	3 (27.3)	0.030
Hydroxychloroquine	11 (100)	8 (72.7)	0.214
Glucocorticoid	8 (72.7)	8 (72.7)	1.000
Prednisolone dose (mg/day)	5.8 (0~14.5)	2.9 (0~11.4)	0.562
Re-infusion of rituximab	1 (9.1)	1 (9.1)	1.000

Data are expressed as median (interquartile range) or number (%). GFR: glomerular filtration rate, N/A: not available.

(83.3% vs. 70.0%, $p=0.624$) was also similar between the two groups.

In the normal GFR group, renal response was achieved in nine patients (CR, eight patients; PR, one patient) at 6 months and 10 patients (all CR) at 12 months. In the decreased GFR group, renal response was achieved in one patient (PR) at 6 months and two patients (all CR) at 12 months. Among nine patients with $\text{UPCR} \geq 3,000$ mg/g, renal response was reported in one of two (50%) patients in the normal GFR group and one of seven (14.3%) patients in the decreased GFR group during 12 months. Among nine patients with $3,000 \text{ mg/g} > \text{UPCR} \geq 1,000$ mg/g, renal response was achieved in five of five (100%) patients in the normal GFR group and one of four (25%) patients in the decreased GFR group. Four patients with $\text{UPCR} < 1,000$ mg/g were in the normal GFR group and achieved renal response.

The overall cumulative renal response rate was 45.5% at 6 months and 54.5% at 12 months (Figure 1). The overall CR rate was 36.4% at 6 months and 54.5% at 12 months. When assessed according to the GFR groups, the cumulative renal response rates at 6 and 12 months were 81.8% and 90.9% in the normal GFR group, respectively, and 9.1% and 18.2% in the decreased GFR group, respectively. Cumulative CR rates at 6 and 12 months were 72.7% and 90.9% in the normal GFR group, respectively, and 0% and 18.2% in the decreased GFR group, respectively. The normal GFR group showed a higher renal response rate than the decreased GFR group (log-rank test, $p < 0.001$). Two patients in the normal GFR group experienced relapse at 6 months. One of them showed improvement after re-in-

fusion of rituximab at 3 months after relapse.

Figure 2 shows changes in clinical parameters from baseline to 12 months in both groups. The median UPCR level had significantly decreased at 12 months in both groups (normal GFR group, from 1,275 [IQR, 920~2,199] to 380 [IQR, 120~426] mg/g, $p=0.003$; decreased GFR group, from 3,110 [IQR, 2,264~5,682] to 1,992 [IQR, 780~3,543] mg/g, $p=0.026$). The median GFR level changed from 116 [IQR, 101~123] to 109 [IQR, 86~111] mL/min/1.73 m² at 12 months in the normal GFR group ($p=0.041$). However, the decreased GFR group exhibited no significant change in the median GFR level from 39 (IQR, 27~79) to 33 (IQR, 22~68) mL/min/1.73 m² at 12 months. The median serum albumin level increased in both groups at 12 months (normal GFR group, from 3.1 to 3.7 g/dL, $p=0.003$; decreased GFR group, from 3.2 to 3.5 g/dL, $p=0.015$). The median SLEDAI-2K score had decreased at 12 months in the normal GFR group (from 12 [IQR, 6~16] to 4 [IQR, 2~6], $p=0.005$), but not in the decreased GFR group (from 8 [IQR, 6~16] to 8 [IQR, 6~12], $p=0.497$). The normal GFR group also showed improved C3, C4, and anti-dsDNA titers at 12 months.

Predictors of renal response to rituximab

The Cox proportional hazard regression analysis of renal response to rituximab was performed (Table 3). In the univariate Cox regression analysis, the normal GFR level (HR=11.331; 95% CI: 2.305~55.710; $p=0.003$), $\text{GFR} \geq 60$ mL/min/1.73 m² (HR=9.534; 95% CI: 1.215~74.823; $p=0.032$), and positive anti-La (HR=10.406;

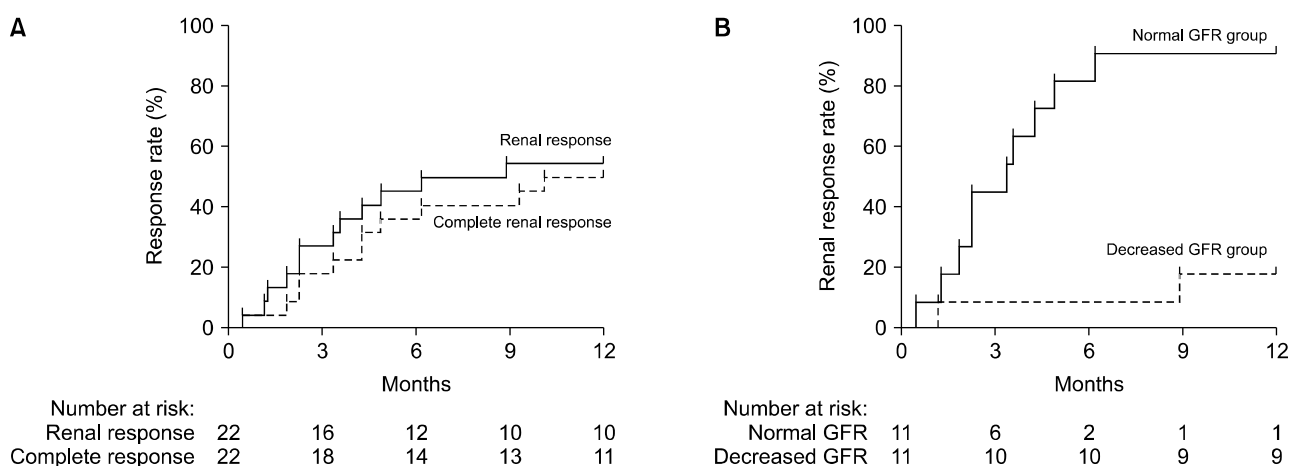


Figure 1. Kaplan-Meier curves for (A) the renal response rate in all patients and (B) renal response rates in normal and decreased glomerular filtration rate groups. Renal response was defined as the achievement of complete or partial renal response. GFR: glomerular filtration rate.

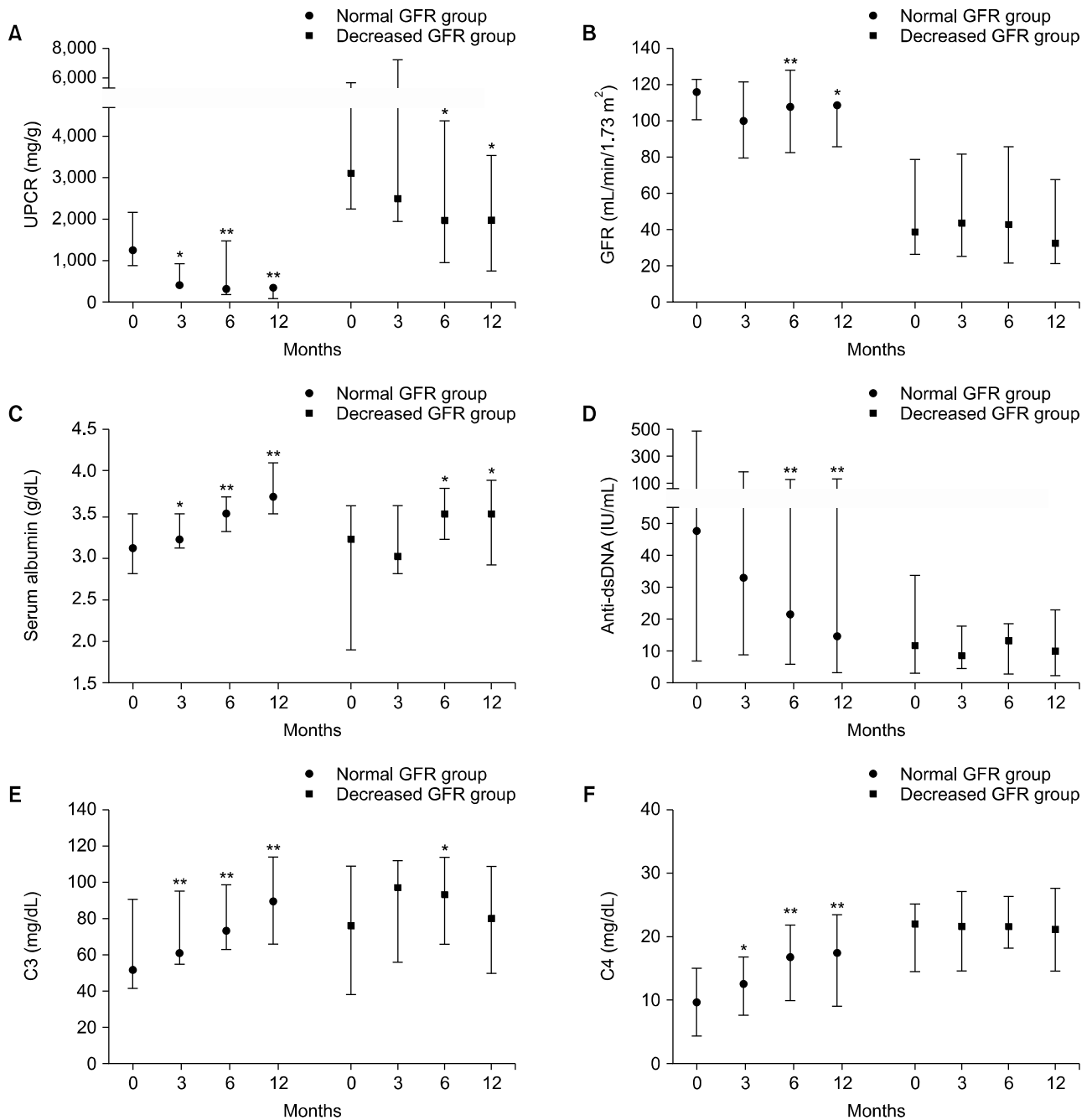


Figure 2. Changes in clinical parameters in normal and decreased glomerular filtration rate groups. (A) Urine protein to creatinine ratio (UPCR). (B) Glomerular filtration rate (GFR). (C) Serum albumin. (D) Anti-dsDNA titer. (E) C3. (F) C4. Data are expressed as median (interquartile range). Wilcoxon signed-rank test was used to assess the changes in parameters from baseline within each group (* $p < 0.05$, ** $p < 0.01$).

95% CI: 2.010~53.878; $p=0.005$) were associated with renal response to rituximab. The levels of C3 (HR=0.976; 95% CI: 0.954~0.999; $p=0.038$) and the history of CYC therapy (HR=0.221; 95% CI: 0.063~0.780; $p=0.019$) negatively correlated with renal response to rituximab. The multivariate Cox regression analysis revealed that the normal GFR level (HR=9.256; 95% CI: 1.767~

48.481; $p=0.008$) and positive anti-La (HR=5.478; 95% CI: 1.072~27.992; $p=0.041$) were statistically significant predictors of renal response to patients with refractory or relapsing LN treated with rituximab.

Table 3. Univariate and multivariate Cox regression analyses for predictors of renal response

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (yr)	0.986	0.947 ~ 1.026	0.485			
Female	1.487	0.191 ~ 11.564	0.705			
Duration since SLE diagnosis (yr)	1.016	0.936 ~ 1.103	0.704			
Duration since LN diagnosis (yr)	0.969	0.866 ~ 1.085	0.588			
ISN/RPS classification						
Class III	1.566	0.495 ~ 4.956	0.446			
Class IV	0.475	0.142 ~ 1.588	0.227			
Class III/V or IV/V	0.215	0.028 ~ 1.671	0.142			
Activity index*	0.899	0.760 ~ 1.062	0.210			
Chronicity index*	0.905	0.690 ~ 1.186	0.468			
Refractory LN (vs. relapsing LN)	0.291	0.078 ~ 1.083	0.066			
Previous immunosuppressants						
Cyclophosphamide	0.221	0.063 ~ 0.780	0.019			
Mycophenolate mofetil	22.295	0.001 ~ 661,999.761	0.555			
Azathioprine	2.061	0.557 ~ 7.626	0.279			
Tacrolimus	0.346	0.071 ~ 1.676	0.187			
Immunosuppressants before the start of rituximab						
Cyclophosphamide	0.367	0.047 ~ 2.858	0.339			
Mycophenolate mofetil	1.676	0.503 ~ 5.584	0.400			
Azathioprine	2.995	0.360 ~ 24.917	0.310			
Tacrolimus	1.791	0.567 ~ 5.654	0.320			
Hydroxychloroquine	2.722	0.350 ~ 21.175	0.339			
Baseline prednisolone dose (mg/day)	1.003	0.972 ~ 1.034	0.872			
Baseline laboratory findings						
Normal GFR level	11.331	2.305 ~ 55.710	0.003	9.256	1.767 ~ 48.481	0.008
GFR ≥ 60 mL/min/1.73 m ²	9.534	1.215 ~ 74.823	0.032			
UPCR (mg/g)	1.000	0.999 ~ 1.000	0.174			
Microscopic hematuria	1.285	0.407 ~ 4.061	0.669			
Serum albumin (g/dL)	0.829	0.379 ~ 1.814	0.640			
C3 (mg/dL)	0.976	0.954 ~ 0.999	0.038			
C4 (mg/dL)	0.938	0.874 ~ 1.007	0.075			
Anti-dsDNA titer (IU/mL)	1.000	0.999 ~ 1.001	0.921			
Anti-ENA positivity [†]						
Anti-RNP	1.857	0.564 ~ 6.114	0.309			
Anti-Sm	1.155	0.337 ~ 3.957	0.819			
Anti-Ro	2.701	0.709 ~ 10.292	0.145			
Anti-La	10.406	2.010 ~ 53.878	0.005	5.478	1.072 ~ 27.992	0.041
Baseline SLEDAI-2K score	1.019	0.915 ~ 1.135	0.729			
Concomitant treatment						
Cyclophosphamide	0.673	0.086 ~ 5.232	0.705			
Mycophenolate mofetil	0.715	0.230 ~ 2.228	0.563			
Azathioprine	2.995	0.360 ~ 24.917	0.310			
Tacrolimus	1.253	0.397 ~ 3.957	0.701			
Cumulative dose of prednisolone (mg/day)	1.035	0.969 ~ 1.106	0.307			

HR: hazard ratio, CI: confidence interval, SLE: systemic lupus erythematosus, LN: lupus nephritis, ISN/RPS: International Society of Nephrology/Renal Pathology Society, GFR: glomerular filtration rate, UPCR: urine protein to creatinine ratio, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000. *Three patients were excluded because of missing data. [†]One patient was excluded because of missing data.

DISCUSSION

We demonstrated that half of the patients treated with

rituximab achieved renal response in refractory or relapsing LN. Patients with normal renal function, defined as GFR ≥ 90 mL/min/1.73 m², showed better renal re-

sponse to rituximab than those with impaired renal function. Most clinical parameters, including proteinuria, improved with 12 months of treatment; however, GFR did not recover. This study suggested that rituximab is a beneficial therapeutic agent in refractory or relapsing LN, particularly when renal function is preserved within the normal range.

The efficacy of rituximab in LN has been investigated in previous studies. The randomized controlled study, Lupus Nephritis Assessment with Rituximab (LUNAR) trial, did not meet the primary endpoint and failed to demonstrate the role of rituximab as an add-on therapy in LN [6]. However, although statistically insignificant, the rituximab group had a 15% increased PR rate compared to the placebo group and reported positive results in terms of proteinuria responses and serologic markers. Several LN studies revealed that rituximab induction and MMF maintenance treatment were effective with the steroid-sparing effect [16,17]. In a study of pathological changes in LN after rituximab therapy, most patients who underwent repeat biopsy after rituximab therapy showed histological transition into a more favorable type with a decreased renal activity index score [18]. These pathologic improvements in LN have been reported in other rituximab studies [19,20]. B lymphocyte depletion occurs after rituximab therapy and is associated with renal response [21,22]. The effects of rituximab on regulatory cells and apoptosis of T lymphocytes in LN have been reported [23]. These clinical, pathological, and immunological results, which differ from randomized controlled trial results, require us to focus on factors associated with renal response to rituximab.

Several previous studies have shown that rituximab may be an alternative therapy in refractory or relapsing LN [7,24-26]. Based on these results, the 2019 Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association guideline recommend rituximab for active non-responding/refractory LN cases [27]. Ethnicity may also affect renal response to rituximab in LN. The prevalence of LN was higher in Asians than in Caucasians, whereas 10-year renal outcomes were better in Asians [28]. The LUNAR trial showed a tendency of improved renal outcomes in Africans compared to individuals of other ethnicities [6]. We reported that 54.5% of Koreans with refractory or relapsing LN achieved renal response in 12 months of rituximab therapy. This result was consistent with a multicenter retrospective study in Korean

patients with SLE, which showed a renal response rate of 65% to rituximab at 6 months [29]. Similarly, a study of Japanese patients with refractory LN reported that 58.8% of patients treated with rituximab achieved a renal response [30]. We suggested the beneficial effects of rituximab in East Asians with refractory or relapsing LN.

As for other clinical information related to the treatment response to rituximab, a pooled analysis study from European cohorts showed that nephrotic syndrome and renal failure at the time of rituximab administration were reported more frequently in patients with no achievement of CR than in those with CR [31]. GFR may be a candidate for predicting renal response to rituximab in LN. GFR and proteinuria are components of LN treatment goals. Proteinuria changes earlier and greater after treatment, whereas GFR changes later in some cases [32]. In a study on renal function as a predictor of LN, patients with $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ showed poor renal outcomes, including ESRD [33]. Dall'Era et al. [34] described that the baseline GFR level predicted renal response to MMF or CYC at 6 months. However, the role of GFR in predicting renal outcome is reported inconsistently. Haridasan et al. [35] found that 70.7% of patients with $\text{GFR} < 30 \text{ mL/min}$ at presentation had good renal response without persistent low GFR or ESRD for 1 year, indicating that renal outcomes may be favorable even in patients with severe renal function. In studies on the efficacy of MMF as induction and maintenance therapy, patients with baseline renal impairment ($\text{GFR} < 60 \text{ mL/min/1.73 m}^2$) had similar renal responses and relapse rates compared to patients with normal renal function [36,37]. In our study, the normal GFR group had better renal responses after rituximab therapy than the decreased GFR group. The multivariate Cox analysis showed that normal renal function at the start of rituximab therapy was associated with the achievement of renal response in patients with refractory or relapsing LN treated with rituximab. The normal GFR group also improved markers of lupus activity, including SLEDAI-2K score, C3, C4, and anti-dsDNA titers. Moreover, our results were supported by a previous LN study, reporting that baseline $\text{GFR} < 30 \text{ mL/min}$ was observed more frequently in renal non-responders than in responders after rituximab treatment [38].

There have been several challenges in the effective use of rituximab in LN, including combination with other immunosuppressants. Zhang et al. [39] showed that combination therapy of rituximab and CYC might be

more beneficial than CYC monotherapy. The combination of rituximab and belimumab also seems a promising treatment to improve lupus activity, with the synergistic effects of B cell depletion and BAFF inhibition [40]. In contrast, a randomized pilot study on the efficacy of rituximab in LN did not prove the improvement of renal response with the addition of CYC [41]. In our study, there were no beneficial effects of combination or sequential therapy with other immunosuppressants. As for the treatment of relapse after rituximab therapy in LN, re-administration of rituximab may help to achieve a good response again. Pepper et al. [16] reported B cell reconstitution in relapsed patients after rituximab therapy. In a study of rituximab therapy in SLE, one patient who experienced recurrence after rituximab therapy had a good response with re-administration of rituximab [42]. We also reported one relapsed patient who had a good renal response with re-administration of rituximab, supporting previous results.

The preferred schedule of rituximab therapy is 1,000 mg on days 0 and 14, which is the regimen used for lymphoproliferative disease and rheumatoid arthritis. However, the optimal regimen, including dose and frequency, has not yet been fully established in LN. Low-dose rituximab therapy (500 mg×2) successfully reduced CD19 B cells for up to 90 days in the nephrology practice [43]. Likewise, a single dose of rituximab 375 mg/m² induced favorable outcomes with prolonged B cell depletion in the refractory LN [44]. A study of membranous nephropathy revealed that the regimen of rituximab 375 mg/m² weekly for 4 weeks depleted more B cell than the regimen of rituximab 1,000 mg twice with a 2-week interval [45]. In addition to these issues, there is a lack of consensus on various strategies for using rituximab, such as maintenance therapy and immunogenicity. Further research is needed on the effective use of rituximab in the treatment of LN.

On the other hand, the autoantibody profile is useful to understand the lupus subtype and predict the outcome in SLE. In LN, the presence of anti-Sm is associated with poor renal outcome [46]. Anti-dsDNA contributes to the pathogenesis of LN by deposition of immune complexes in mesangial matrix and binding exposed chromatin fragments in glomerular basement membrane [47]. We found that the positive anti-La was also associated with good renal response of rituximab. This result is consistent with the previous opinion that anti-La has a protective effect from LN [48].

There were some limitations to this study. First, the

sample size was small. Second, this was a retrospective study performed at a single center. Third, some baseline characteristics differed between the groups, possibly affecting the renal response. However, the multivariate Cox analysis was used to adjust the influence of other clinical values and identify the effect of GFR. Finally, we used estimated GFR in this study, which may not reflect the actual GFR in some cases. Within these limitations, this study showed an association between renal function at the start of rituximab therapy and renal response in refractory or relapsing LN.

CONCLUSION

Patients with refractory or relapsing LN treated with rituximab achieved good renal response in 12 months. Those with preserved renal function at the start of rituximab therapy had better renal response than those with renal impairment. This result may provide useful information in determining rituximab therapy in patients with refractory or relapsing LN based on renal function.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

S.H., C.K.L., B.Y., and Y.G.K. were involved in conception and design of study. S.J.C., S.M.A., J.S.O., and Y.G.K. were contributed to acquisition, analysis and interpretation of data. All authors were involved in drafting and revising the manuscript critically for important intellectual content and final approval of the version to be published.

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