Factors associated with aggravation of tubulointerstitial damage on repeated biopsies in lupus nephritis patients with treatment failure

O.C. Kwon[1,2], Y.M. Cho[3], J.S. Oh[4], S. Hong[1], C.-K. Lee[1], B. Yoo[1], Y.-G. Kim[1]

[1]Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul; [2]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul; [3]Department of Pathology, [4]Department of Biomedical Informatics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

Abstract

Objective

Tubulointerstitial damage in lupus nephritis (LN) is an important predictor of renal prognosis. Here, we investigated the factors associated with aggravation of tubulointerstitial damage in patients with LN.

Methods

Patients with LN, who underwent repeated renal biopsy due to treatment failure at a tertiary referral hospital between 1997 and 2017 were identified. Clinicopathologic and laboratory data were collected. Aggravation of tubulointerstitial damage (tubular atrophy and/or interstitial fibrosis) was defined as progression of severity from none-to-mild to moderate-to-severe. Factors associated with aggravation of tubulointerstitial damage were evaluated using logistic regression analysis.

Results

A total of 52 LN patients were included for analysis. Aggravation of tubulointerstitial damage at the second renal biopsy was observed in 19 (36.5%) patients. In multivariable logistic regression analysis, use of hydroxychloroquine (adjusted OR 0.215, 95% CI 0.049–0.941, p=0.041) was inversely associated with aggravation of tubulointerstitial damage, and higher renal component of systemic lupus erythematosus disease activity index (SLEDAI) at first biopsy (adjusted OR 1.331, 95% CI 1.083–1.636, p=0.007) was associated with aggravation of tubulointerstitial damage. In terms of use of HCQ, both length of treatment with HCQ (adjusted OR 0.974, 95% CI 0.951–0.998, p=0.036) and cumulative dose of HCQ (log transferred value) (adjusted OR 0.485, 95% CI 0.262–0.896, p=0.020) were inversely associated with aggravation of tubulointerstitial damage.

Conclusion

Use of hydroxychloroquine was associated with lower risk of aggravation in tubulointerstitial damage, and higher renal component of SLEDAI at first renal biopsy was associated with higher risk of aggravation in tubulointerstitial damage.

Key words

systemic lupus erythematosus, lupus nephritis, tubulointerstitial damage

Oh Chan Kwon, MD
Yong Mee Cho, MD, PhD
Ji Seon Oh, MD, PhD
Seokchan Hong, MD, PhD
Chang-Keun Lee, MD, PhD
Bin Yoo, MD, PhD
Yong-Gil Kim, MD, PhD

Please address correspondence to:
Yong-Gil Kim,
Division of Rheumatology,
Department of Internal Medicine,
University of Ulsan, College of Medicine,
Asan Medical Center,
88 Olympic-ro 43-gil,
Songpa-gu, Seoul 05505, Korea.
E-mail: bestmd2000@amc.seoul.kr

Received on February 12, 2019; accepted in revised form on May 20, 2019.

Funding: this work was supported by a grant [2019-463] from the Asan Institute for Life Sciences, Asan Medical Center, Korea.

Competing interests: none declared.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, that affects multiple types of tissues and organs (1). Lupus nephritis (LN), one of the common manifestations of SLE, causes significant morbidity and mortality in patients with SLE (2). LN may manifest as the presence of hematuria, proteinuria, or decreased renal function, and for confirmatory diagnosis, renal biopsy is required (3). Based on glomerular pathology, LN is currently classified using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification standards (4). The American College of Rheumatology (ACR) and the Joint European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association guidelines recommend treatments for LN according to the ISN/RPS 2003 classification (5, 6). Despite the strategic treatment based on these guidelines and advances in immunosuppressive treatments, 10–20% of patients still progress into end-stage renal disease (ESRD), and up to 40% of patients develop some degree of renal impairment (3, 7, 8).

Although patients with LN are treated based on glomerular lesions, glomerular parameters are poor predictors of ESRD (9). Indeed, a number of studies have shown that tubulointerstitial damage is better at predicting renal survival than glomerular lesions (3, 9, 10). Moreover, tubulointerstitial damage is considered an independent risk factor for the development of ESRD, regardless of the degree of glomerular damage (10). Considering the importance the tubulointerstitial damage has on renal prognosis, it is crucial to identify factors associated with the aggravation of tubulointerstitial damage, which are not well-characterised to date. We thus aimed to identify factors associated with aggravation of tubulointerstitial damage in patients with LN.

Materials and methods

Study population

We retrospectively reviewed the medical records of patients who were diagnosed with LN by renal biopsy between January 1997 and September 2017 at Asan Medical Center, a tertiary referral hospital in Seoul, Korea. Patients who underwent repeated renal biopsies during the course of their disease were included. Second renal biopsies were performed in the following indications: (i) persistent proteinuria, (ii) renal flare, which was defined as a ≥10% decrease in GFR, active appearance of urine sediments, or an increase of urine protein/creatinine ratio (uPCR) to more than 1000 mg/g, after achieving complete renal response (6). For patients who underwent renal biopsy prior to the application of ISN/RPS 2003 classification, their biopsy results were reclassified according to the ISN/RPS 2003 classification. All patients met the 1997 ACR classification criteria for SLE (11). The Institutional Review Board of Asan Medical Center in Seoul, South Korea approved this study (IRB no: 2018-0137). Due to the retrospective nature of this study, the requirement for informed consent was waived.

Clinical, laboratory, and pathologic parameters

The following clinical and laboratory data at first renal biopsy were collected: age, sex, presence of hypertension and diabetes mellitus, time from SLE to LN diagnosis, uPCR, urinalysis results, serum albumin level, serum creatinine level, estimated glomerular filtration rate (GFR), C3, C4, autoantibody profile, and SLE Disease Activity Index (SLEDAI) (12). The cut-off values used for positivity of autoantibodies were as follows: anti-Sm Ab, 10 U/ml; anti-Ro Ab, 10 U/ml; anti-La Ab, 10 U/ml; anti-RNP Ab, 10 U/ml; anti-cardiolipin Ab, 40 GPL/ml (for IgG) or 40 MPL/ml (for IgM); anti-beta2 glycoprotein 1 Ab, 40 G units (for IgG) or 40 M units (for IgM). For analysis, SLEDAI was dissected into renal component and non-renal component.

In terms of pathologic data, ISN/RPS 2003 classification, activity index, chronicity index, and severity of tubulointerstitial inflammation, tubular atrophy, interstitial fibrosis, and glomerulosclerosis at first and second renal biopsies were reviewed. The severity levels of tubulointerstitial inflammation and tubulointerstitial damage (tubular atrophy

and/or interstitial fibrosis) were graded based on light microscopic exam with histological staining. Stains used included haematoxylin and eosin, periodic acid-Schiff, silver methenamine, and Massons' trichrome. The severity levels of tubulointerstitial inflammation and tubulointerstitial damage were classified as either none (0% of the acreage of interstitium affected), mild (<25% of the acreage of interstitium affected), moderate (25–50% of the acreage of interstitium affected), or severe (>50% of the acreage of interstitium affected) (9, 10). For the analysis, these tubulointerstitial indices were categoried into dichotomous variables (none-to-mild *vs*. moderate-to-severe). The severity of glomerulosclerosis was assessed as the proportion of sclerotic glomeruli to total glomeruli. Pathologic parameters were reviewed by a pathologist without prior knowledge of the clinical outcomes.

Medications used between the first and second biopsies were also reviewed. Hydroxychloroquine (HCQ), mycophenolate mofetil, cyclophosphamide (CYC), azathioprine, tacrolimus, cyclosporine, rituximab, angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, and glucocorticoids were prescribed. Use of medications between the two time points was categorised as either "ever used" or "never used". For induction therapy, patients received cyclophosphamide according to the National Institutes of Health protocol (13) or mycophenolate mofetil (2–3 g/day) (14) in addition to moderate-to-high dose glucocorticoid. Patients who failed to respond were switched from cyclophosphamide to mycophenolate mofetil (and vice versa), or were received rituximab in some cases. For maintenance therapy, azathioprine, cyclosporine, mycophenolate mofetil, or tacrolimus with low dose glucocorticoid was used. The time interval between the first and second biopsies varied among patients, while the dose of glucocorticoid varied among patients mostly during the first year after the first biopsy. Therefore, for patients using glucocorticoids, the cumulative dose during the first year after the first biopsy was evaluated.

For patients who received immunosuppressive agents (all 31 patients with class III LN and class IV LN and 10 of 13 patients with class V LN), renal response at 6 months after induction therapy were checked. Complete renal response was defined as uPCR <500 mg/g and normal or near normal GFR and partial renal response was defined as ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR (6).

Table I. Histologic characteristics of the 53 patients.

Histologic characteristics		1st biopsy	2nd biopsy
ISN/RPS class	II	9 (17.0%)	1 (1.9%)
	III ± V	10 (18.9%)	12 (22.6%)
	IV ± V	21 (39.6%)	30 (56.6%)
	V	13 (24.5%)	8 (15.1%)
	VI	0 (0.0%)	2 (3.8%)
Activity index		2.0 (1.0–7.0)	5.0 (2.0–8.0)
Chronicity index		1.0 (0.0–2.0)	3.0 (2.0–5.5)
TII	none-to-mild	50 (94.3%)	33 (62.3%)
	moderate-to-severe	3 (5.7%)	20 (37.7%)
Renal scarring (TA/IF)	none-to-mild	52 (98.1%)	34 (64.2%)
	moderate-to-severe	1 (1.9%)	19 (35.8%)
Glomerulosclerosis (%)		0.0 (0.0–7.2)	38.2 (12.7–62.6)

ISN/RPS: International Society of Nephrology/Renal Pathology Society; TII: tubulointerstitial inflammation; TA: tubular atrophy; IF: interstitial fibrosis.

Definition of aggravation of tubulointerstitial damage

Aggravation of tubulointerstitial damage was defined as progression of severity of tubular atrophy and/or interstitial fibrosis from none-to-mild to moderate-to-severe. Patients with moderate-to-severe tubulointerstitial damage at first renal biopsy were excluded from analysis because aggravation of tubulointerstitial damage could not be defined in those patients.

Statistical analysis

To summarise patient characteristics, continuous variables were expressed as median (interquartile range [IQR]). Categorical variables were expressed as number (%). For comparison between two groups, the Mann-Whitney test was used for continuous variables, and Fisher's exact test and Chi-square test (when appropriate) were used for categorical variables. Multivariable logistic regression analysis with stepwise backward elimination was used to identify factors associated with aggravation of tubulointerstitial damage. Factors with a *p*-value less than 0.05 in the univariable analysis were included in the multivariable analysis. For variables included in the multivariable analysis, no multicollinearity was detected among variables. SPSS software (SPSS v. 20.0, Armonk, NY, IBM Corporation) was used to conduct all analyses.

Results

Patient characteristics

A total of 53 patients with LN who underwent repeated biopsies were identified. Thirty-five (66.0%) patients were female and the median age was 24 (14.5–34.5) years. The median time from SLE diagnosis to first renal biopsy was 0.0 (0.0–14.5) months. The median time interval between the first and second renal biopsy was 66.5 (37.6–94.9) months. In total, 19 (35.8%) patients underwent second biopsies due to persistent proteinuria, and the other 34 (64.2%) patients underwent second biopsies due to renal flare. Histologic characteristics at the first and second biopsies are summarised in Table I.

Comparisons between the patients who experienced aggravation of tubulointerstitial damage and those who did not are shown in Table II. Of the total 53 patients, one patient with moderate-to-severe tubulointerstitial damage at first renal biopsy was excluded and the remaining 52 patients who had none-to-mild tubulointerstitial damage at first renal biopsy were included for analy-

sis. Aggravation of tubulointerstitial damage at the second renal biopsy was observed in 19 (36.5%) patients. Compared to patients who did not experience aggravation of tubulointerstitial damage, patients who experienced aggravation of tubulointerstitial damage had higher frequency of haematuria (100.0% *vs*. 60.6%, *p*=0.002), lower frequency of anti-Sm antibody (21.4% *vs*. 53.6%, *p*=0.047) and anti-RNP antibody (7.1% *vs*. 57.7%, p=0.002), higher SLEDAI (renal component) (12.0 (8.0–12.0) *vs*. 8.0 (4.0–12.0), *p*=0.005) and activity index (3.0 (1.0–10.0) *vs*. 1.0 (0.0–4.5), *p*=0.019), lower frequency of HCQ usage (57.9% *vs*. 84.8%, *p*=0.047) and higher frequency of CYC usage (84.2% *vs*. 57.6%, *p*=0.049). The higher frequency of CYC usage in patients who experienced aggravation of tubulointerstitial damage may be due to the numerically higher proportion of patients with proliferative LN (class III and IV) in this group, although statistically not significant (73.7% *vs*. 51.5%, *p*=0.117). The duration of cyclophosphamide used did not differ between the 2 groups (5.5 (4.0–6.0) months *vs*. 6.0 (4.0–6.0) months, *p*=0.945).

Factors associated with aggravation of tubulointerstitial damage

Factors associated with aggravation of tubulointerstitial damage are shown in Table III. In univariable analysis, higher SLEDAI (renal component) (unadjusted odds ratio [OR] 1.318, 95% confidence interval [CI] 1.080–1.609, *p*=0.007), activity index (unadjusted OR 1.166, 95% CI 1.007–1.349, *p*=0.039), and one-year cumulative dose of glucocorticoid (unadjusted OR 1.224, 95% CI 1.002–1.495, *p*=0.048) were associated with higher risk of aggravation of tubulointerstitial damage, whereas use of HCQ (unadjusted OR 0.246, 95% CI 0.066–0.917, *p*=0.037) was associated with lower risk of aggravation of tubulointerstitial damage. In multivariable analysis with stepwise backward elimination, SLEDAI (renal component) (adjusted OR 1.331, 95% CI 1.083–1.636, *p*=0.007) and use of HCQ (adjusted OR 0.215, 95% CI 0.049–0.941, *p*=0.041) remained as statistically significant.

Table II. Comparison of baseline characteristics at first renal biopsy between patients who did and did not experience aggravation of tubulointerstitial damage.

	Aggravation (n=19)	No aggravation (n=33)	*p*-value
Female	13 (68.4%)	22 (66.7%)	0.897
Age (years)	20.0 (13.0–28.0)	28.0 (17.5–36.5)	0.177
Hypertension	5 (26.3%)	8 (24.2%)	>0.999
Diabetes mellitus	3 (15.8%)	1 (3.0%)	0.132
Time from SLE to LN (months)	0.0 (0.0–6.0)	0.0 (0.0–23.5)	0.327
Time interval between first and second renal biopsies (months)	57.5 (40.2–91.3)	70.3 (37.2–99.9)	0.902
uPCR (mg/g)	1916.0 (1047.5–4881.3)	1665.0 (1063.4–5003.0)	0.794
Urine WBC ≥ 3-5/HPF	10 (52.6%)	14 (42.4%)	0.477
Urine RBC ≥ 3-5/HPF	19 (100.0%)	20 (60.6%)	**0.002**
Serum albumin (g/dl)	2.6 (1.8–3.1)	2.9 (2.1–3.4)	0.356
Creatinine (mg/dl)	0.8 (0.6–1.2)	0.7 (0.6–0.9)	0.220
GFR (ml/min/1.73 m^2)	92.0 (54.5–128.0)	108.0 (90.5–119.0)	0.372
C3 (mg/dl)	32.2 (21.3–56.1)	39.9 (27.2–68.7)	0.328
C4 (mg/dl)	5.7 (1.8–11.2)	4.5 (1.9–13.0)	0.894
Anti-dsDNA Ab (IU/ml)	316.0 (23.1–2990.0)	20.0 (8.7–375.0)	0.085
Anti-Sm Ab (*n=42)	3 (21.4%)	15 (53.6%)	**0.047**
Anti-Ro Ab (*n=43)	5 (33.3%)	18 (64.3%)	0.052
Anti-La Ab (*n=43)	3 (20.0%)	5 (17.9%)	>0.999
Anti-RNP Ab (*n=40)	1 (7.1%)	15 (57.7%)	**0.002**
Lupus anticoagulant (*n=47)	3 (15.8%)	9 (32.1%)	0.310
Anti-cardiolipin Ab (*n=47)	6 (35.3%)	12 (40.0%)	0.750
Anti-beta2 glycoprotein 1 Ab (*n=38)	3 (25.0%)	4 (15.4%)	0.656
SLEDAI (renal component)	12.0 (8.0–12.0)	8.0 (4.0–12.0)	**0.005**
SLEDAI (non-renal component)	6.0 (3.0–8.0)	5.0 (4.0–6.0)	0.862
ISN/RPS class III	6 (31.6%)	4 (12.1%)	0.142
ISN/RPS class IV	8 (42.1%)	13 (39.4%)	>0.999
ISN/RPS class III and class IV	14 (73.7%)	17 (51.5%)	0.117
Activity index	3.0 (1.0–10.0)	1.0 (0.0–4.5)	**0.019**
Chronicity index	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.218
Moderate-to-severe TII	1 (5.3%)	1 (3.0%)	>0.999
Glomerulosclerosis (%)	0.0 (0.0–8.3)	0.0 (0.0–5.9)	0.915
Hydroxychloroquine	11 (57.9%)	28 (84.8%)	**0.047**
Cyclophosphamide	16 (84.2%)	19 (57.6%)	**0.049**
Duration of use (months)	5.5 (4.0–6.0)	6.0 (4.0–6.0)	0.945
Azathioprine	14 (73.7%)	20 (60.6%)	0.340
Mycophenolate mofetil	12 (63.2%)	13 (39.4%)	0.099
Tacrolimus	7 (36.8%)	17 (51.5%)	0.307
Cyclosporine	4 (21.1%)	3 (9.1%)	0.400
Rituximab	2 (10.5%)	2 (6.1%)	0.617
ACEi or ARB	18 (94.7%)	30 (90.9%)	>0.999
One-year cumulative dose of glucocorticoid (g)	7.26 (5.12–9.98)	6.15 (4.54–7.72)	0.136
Complete renal response at 6 months after induction therapy (†n=41)	4 (22.2%)	11 (47.8%)	0.091
Partial renal response at 6 months after induction therapy (†n=41)	9 (50.0%)	7 (30.4%)	0.202

SLE: systemic lupus erythematosus; LN: lupus nephritis; uPCR: urine protein/creatinine ratio; WBC: white blood cell; RBC: red blood cell; GFR: glomerular filtration rate; anti-dsDNA Ab: anti-double-stranded DNA antibody; SLEDAI: systemic lupus erythematosus disease activity index; ISN/RPS: International Society of Nephrology/Renal Pathology Society; TII: tubulointerstitial inflammation; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.
*Patients with missing data were excluded.
†Patients who did not receive immunosuppressive agents were excluded.

Longitudinal effect of hydroxychloroquine on tubulointerstitial damage

For the 39 patients who were classified as HCQ users, 12 patients were started on HCQ before first renal biopsy and 25 patients were started on HCQ at first renal biopsy. The other 2 patients started on HCQ during the follow up period. Five patients stopped HCQ during the follow up period because of deterioration of renal function, and the remaining 34 patients were maintained

Table III. Factors associated with aggravation of tubulointerstitial damage.

	Univariable analysis			Multivariable analysis		
	Unadjusted OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Female	1.083	0.324–3.626	0.897			
Age	0.980	0.939–1.023	0.357			
Hypertension	1.116	0.306–4.074	0.868			
Diabetes mellitus	6.000	0.577–62.374	0.134			
Time interval between first and second renal biopsies (months)	1.000	0.989–1.011	0.968			
uPCR	0.962	0.835–1.108	0.592			
Urine WBC ≥ 3-5/HPF	1.508	0.485–4.690	0.478			
Urine RBC ≥ 3-5/HPF	N/A	N/A	0.998			
Serum albumin	0.690	0.312–1.524	0.358			
Creatinine	1.065	0.673–1.686	0.789			
GFR	0.987	0.970–1.004	0.130			
C3	0.996	0.972–1.019	0.712			
C4	1.016	0.949–1.088	0.650			
Anti-dsDNA Ab	1.026	0.988–1.065	0.182			
SLEDAI (renal component)	1.318	1.080–1.609	**0.007**	1.331	1.083–1.636	**0.007**
SLEDAI (non-renal component)	1.049	0.862–1.276	0.632			
ISN/RPS class III	3.346	0.805–13.903	0.096			
ISN/RPS class IV	1.119	0.355–3.525	0.848			
ISN/RPS class III and class IV	2.635	0.772–9.001	0.122			
Activity index (glomerular component)	1.166	1.007–1.349	**0.039**	1.038	0.866–1.243	0.689
Chronicity index (glomerular component)	1.335	0.858–2.078	0.201			
Moderate-to-severe TII	1.778	0.105–30.165	0.690			
Glomerulosclerosis	1.021	0.960–1.085	0.513			
Use of Hydroxychloroquine	0.246	0.066–0.917	**0.037**	0.215	0.049–0.941	**0.041**
Use of Cyclophosphamide	3.930	0.956–16.148	0.058			
Use of Azathioprine	1.820	0.528–6.271	0.343			
Use of Mycophenolate mofetil	2.637	0.823–8.452	0.103			
Use of Tacrolimus	0.549	0.173–1.743	0.309			
Use of Cyclosporine	2.667	0.528–13.477	0.235			
Use of Rituximab	1.824	0.235–14.126	0.565			
Use of ACEi or ARB	1.800	0.174–18.638	0.622			
One-year cumulative dose of glucocorticoid	1.224	1.002–1.495	**0.048**	1.117	0.895–1.394	0.327

OR: odds ratio; CI: confidence interval; uPCR; urine protein/creatinine ratio; WBC: white blood cell; RBC: red blood cell; GFR: glomerular filtration rate; anti-dsDNA Ab: anti-double-stranded DNA antibody; SLEDAI: systemic lupus erythematosus disease activity index; ISN/RPS: International Society of Nephrology/Renal Pathology Society; TII: tubulointerstitial inflammation; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

Table IV. Longitudinal effect of hydroxychloroquine on aggravation of tubulointerstitial damage.

	Multivariable analysis*		
	Adjusted OR	95% CI	*p*-value
Use of HCQ	0.158	0.030–0.824	**0.029**
Length of HCQ use (months)	0.974	0.951–0.998	**0.036**
Cumulative dose of HCQ (log transferred value)	0.485	0.262–0.896	**0.020**

OR: odds ratio; CI: confidence interval; HCQ; hydroxychloroquine.
*Adjusted for SLEDAI (renal component), activity index (glomerular component), and 1-year cumulative dose of glucocorticoid.

on HCQ at second renal biopsy. During the follow up period (time interval between first and second renal biopsies: 66.5 (37.6–94.9) months), the median duration of HCQ use in HCQ users was 62.5 (35.9–81.2) months and the median cumulative dose of HCQ was 461.6 (281.6–800.6) g.

To evaluate the longitudinal effect of HCQ on tubulointerstitial damage, we analysed the odds ratio of aggravation of tubulointerstitial damage in patients who were started on HCQ at first renal biopsy (n=25), compared to the patients who were never started on HCQ (n=13). In multivariable analysis (adjusted for factors with a *p*-value <0.05 in univariable analysis: SLEDAI [renal component], activity index [glomerular component], and 1-year cumulative dose of glucocorticoid), use of HCQ (adjusted OR 0.158, 95% CI 0.030–0.824, *p*=0.029), length of treatment with HCQ (adjusted OR 0.974, 95% CI 0.951–0.998, *p*=0.036) and cumulative dose of HCQ (log transferred value) (adjusted OR 0.485, 95% CI 0.262–0.896, *p*=0.020) during the follow up period were inversely associated with aggravation of tubulointerstitial damage (Table IV).

Discussion

In this retrospective longitudinal study in a cohort of patients with LN who underwent repeated renal biopsies, we found that use of HCQ was significantly associated with a lower risk of aggravation of tubulointerstitial damage. Further, higher renal component of SLEDAI at first biopsy was associated with higher risk of aggravation of tubulointerstitial damage. To the best of our knowledge, this is the first study to identify factors associated with aggravation of tubulointerstitial damage, particularly in a longitudinal design.

In our study, the prevalence of moderate-to-severe tubulointerstitial damage at first renal biopsy was relatively low compared with those of previous reports (15, 16). One possible explanation for this finding is that patients included in our study had short disease duration at first renal biopsy. Time from SLE to first renal biopsy was median 0.0 (0.0–14.5) month in our patients. We did, however, observe that tubulointerstitial damages became more severe in some patients during the course of disease, which is consistent with the results of previous studies (15, 17). Given the importance of persistent tubulointersti-

tial damage on renal survival (17), the factors associated with aggravation of tubulointerstitial damage outlined in this study are noteworthy.

Previous studies have shown that the use of HCQ is associated with a reduced risk of renal damage and is effective for achieving renal remission in LN (18, 19). However, these studies did not address the effect of HCQ on tubulointerstitial damage. Recently, a cross-sectional retrospective study showed that the use of HCQ was inversely associated with severity of tubulointerstitial inflammation (16). Our longitudinal data adds to this previous finding by showing that both length of treatment with HCQ and cumulative dose of HCQ are inversely associated with aggravation of tubulointerstitial damage. Therefore, HCQ may be an effective medication for managing not only tubulointerstitial inflammation but also tubulointerstitial damage.

A positive correlation between SLEDAI and immune complex deposition in tubular basement membrane had been recently reported (20). Moreover, deposition of immune complex in tubular basement membrane was positively correlated with severity of tubulointerstitial damage (20). Notably, association between renal component of SLEDAI at first renal biopsy and aggravation of tubulointerstitial damage was observed in our study. Although causality cannot be stated, this association might be explained by the higher burden of immune complex deposition in tubular basement membrane in patients with higher renal component of SLEDAI.

Our study has several limitations. First, we only included patients who underwent repeated biopsies, which were performed due to clinical indications such as renal flare or persistent proteinuria. Because there are no reliable markers of tubulointerstitial damage, aggravation of tubulointerstitial damage may have been undetected in patients who lacked clinical indications that called for renal biopsy. The results of our current study cannot be generalised to such patients. Second, the activity index at first biopsy was low (median activity index = 2.0), which may limit the generalisation of our results. Third, this was a retrospective study. Although we identified factors associated with aggravation in tubulointerstitial damage, causality cannot be drawn from our data because of the retrospective study design. Furthermore, there may be confounding factors not included in our analysis. Fourth, our sample size did not allow for drawing a sufficiently powerful conclusion. A prospective controlled study with larger sample size is needed to validate our current results. In summary, the use of HCQ was associated with lower risk of aggravation of tubulointerstitial damage. Higher renal component of SLEDAI was associated with higher risk of aggravation of tubulointerstitial damage. Our hypothesis-generating study suggests that patients with higher renal component of SLEDAI at their first renal biopsy should be carefully monitored for further aggravation of tubulointerstitial damage, and if not contraindicated, HCQ should be used even after initiating immunosuppressive treatment.

Acknowledgements

This work was supported by a grant [2019-463] from the Asan Institute for Life Sciences, Asan Medical Center, Korea.

References

1. LISNEVSKAIA L, MURPHY G, ISENBERG D: Systemic lupus erythematosus. *Lancet* 2014; 384: 1878-88.
2. BERNATSKY S, BOIVIN JF, JOSEPH L *et al*.: Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006; 54: 2550-7.
3. YU F, HAAS M, GLASSOCK R, ZHAO MH: Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. *Nat Rev Nephrol* 2017; 13: 483-95.
4. WEENING JJ, D'AGATI VD, SCHWARTZ MM *et al*.: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15: 241-50.
5. HAHN BH, MCMAHON MA, WILKINSON A *et al*.: American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res* (Hoboken) 2012; 64: 797-808.
6. BERTSIAS GK, TEKTONIDOU M, AMOURA Z *et al*.: Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR / ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012; 71: 1771-82.
7. CONTRERAS G, PARDO V, CELY C *et al*.: Factors associated with poor outcomes in patients with lupus nephritis. *Lupus* 2005; 14: 890-5.
8. HOUSSIAU FA, LAUWERYS BR: Current management of lupus nephritis. *Best Pract Res Clin Rheumatol* 2013; 27: 319-28.
9. HSIEH C, CHANG A, BRANDT D, GUTTIKONDA R, UTSET TO, CLARK MR: Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. *Arthritis Care Res (Hoboken)* 2011; 63: 865-74.
10. YU F, WU LH, TAN Y *et al*.: Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. *Kidney Int* 2010; 77: 820-9.
11. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
12. GLADMAN DD, IBANEZ D, UROWITZ MB: Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29: 288-91.
13. AUSTIN HA, 3RD, KLIPPEL JH, BALOW JE *et al*.: Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; 314: 614-9.
14. CHAN TM, LI FK, TANG CS *et al*.: Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 2000; 343: 1156-62.
15. PAGNI F, GALIMBERTI S, GALBIATI E *et al*.: Tubulointerstitial lesions in lupus nephritis: International multicentre study in a large cohort of patients with repeat biopsy. *Nephrology* (Carlton) 2016; 21: 35-45.
16. LONDONO JIMENEZ A, MOWREY WB, PUTTERMAN C, BUYON J, GOILAV B, BRODER A: Tubulointerstitial damage in lupus nephritis: a comparison of the factors associated with tubulointerstitial inflammation and renal scarring. *Arthritis Rheumatol* 2018:
17. ALSUWAIDA AO: Interstitial inflammation and long-term renal outcomes in lupus nephritis. *Lupus* 2013; 22: 1446-54.
18. FESSLER BJ, ALARCON GS, MCGWIN G, JR *et al*.: Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis Rheum* 2005; 52: 1473-80.
19. KASITANON N, FINE DM, HAAS M, MAGDER LS, PETRI M: Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. *Lupus* 2006; 15: 366-70.
20. WANG H, XU J, ZHANG X *et al*.: Tubular basement membrane immune complex deposition is associated with activity and progression of lupus nephritis: a large multicenter Chinese study. *Lupus* 2018; 27: 545-55.