Advanced Chronic Kidney Disease in Lupus Nephritis: Is Dialysis Inevitable?

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ABSTRACT. ***Objective.*** Advanced chronic kidney disease (CKD) carries an increased risk for progression to endstage renal disease (ESRD). We aimed to determine the rate of progression and the factors that drive the decline of renal function in lupus nephritis (LN).

Methods. Patients with advanced LN-related CKD were identified from our longterm longitudinal cohort. Advanced CKD was defined as stage 3b [estimated glomerular filtration rate (eGFR) = 30–44 ml/min/1.73 m^2] and stage 4 (eGFR = 15–29 ml/min/1.73 m^2). All individuals were followed until progression to ESRD or the last visit and were divided into "progressors" and "non-progressors." Demographic, clinical, immunological, and therapeutic variables were compared at baseline. Multivariable Cox regression analysis (both time-dependent and independent) was performed to identify predictors for progression.

Results. One hundred eighteen patients (74 CKD 3b and 44 CKD 4) were included. Forty-five patients progressed (29 to ESRD and 16 from CKD 3b to CKD 4) after 6 years on average. No significant decline in the renal function was observed in 73 patients ("non-progressors") after 10 years on average. Active serology (high anti-dsDNA titers and low complements C3/C4) at the time of CKD diagnosis and any increase of the daily prednisone dose after baseline were strongly associated with progression. Treatment with renin angiotensin system (RAS) blockers was associated with less risk for progression.

Conclusion. Dialysis is not inevitable in LN-related advanced CKD because 62% of our patients did not progress over 10 years of followup on average. Certain predictors were identified to affect progression to ESRD. (J Rheumatol First Release June 15 2020; doi:10.3899/jrheum.191064)

Key Indexing Terms:
LUPUS NEPHRITIS ADVANCED KIDNEY DISEASE PROGRESSION

Lupus nephritis (LN) affects nearly 40% of patients with systemic lupus erythematosus (SLE) with the majority of the cases (80%) diagnosed upon presentation[1]. Despite the advances in the management of LN during the past 2 decades[2], the 10-year incidence of endstage renal disease (ESRD) was 10.1% in a multiethnic inception cohort[1]. In a metaanalysis of 18,309 patients worldwide, Tektonidou, *et al* reported that the 10-year incidence of ESRD was significantly decreased from the 1970s to the mid-1990s and then plateaued to a level of 17% in developed countries[3]. Diffuse proliferative LN (class IV) had the worst outcome with a 10-year incidence of ESRD equal to 33% that climbed to 44% at 15 years[3]. In that metaanalysis, studies that had enrolled patients with advanced chronic kidney disease (CKD; no specific definition was provided) were excluded because the rate of progression to ESRD is distinctly greater[4]. Moreover, such patients are significantly underrepresented or even excluded from the usual protocols of the clinical trials[5,6,7], on the assumption that progression to more severe stages of kidney insufficiency is inevitable. Indeed, a subgroup analysis of 32 (out of 370) patients with poor kidney function [as defined by an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2] of the Aspreva Lupus Management Study showed that the response rate was about 20% at 24 weeks[8]. This was substantially smaller than the overall 55% of response in the initial study[6].

Thus there is a paucity of information regarding advanced CKD in LN. The aim of our present study was to assess the characteristics and outcomes of patients with advanced LN-related CKD with a particular emphasis on the rate of the decline of renal function and its associated factors.

MATERIALS AND METHODS

At the time of our study, the University of Toronto Lupus Clinic (UTLC) had enrolled 1954 patients since its establishment in 1970. All patients fulfilled the revised American College of Rheumatology criteria for the classification of SLE[9] or had 3 criteria and a supportive kidney biopsy.

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Patients are followed regularly at intervals of 2–6 months according to a standardized research protocol, which is regularly updated. This protocol records demographic, clinical, immunological, and therapeutic variables as well as most comorbidities.

For the purpose of our present study, patients with advanced CKD due to LN (based on renal biopsy) were identified from the database. CKD was defined as stage 3b (moderately to severely decreased kidney function) and stage 4 (severely decreased kidney function) according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 definitions[4]. Enrollment was based on 2 consecutive clinic visits with eGFR = 30–44 ml/min/1.73 m^2 for stage 3b and eGFR = 15–29 ml/min/1.73 m^2 for stage 4. The calculation of eGFR was based on the Modification of Diet in Renal Disease formula in the absence of any acute illness.

Patients were divided into "progressors" and "non-progressors" according to the progression to more severe stages of kidney insufficiency [transition to ESRD (defined as eGFR < 15 ml/min/1.73 m^2 or initiation of dialysis) or from stage 3b to stage 4]. The time frame of the study was from baseline (second visit with advanced CKD) up to the last visit or initiation of dialysis. Baseline variables that were compared between groups included demographics (age, sex, race/ethnicity, disease duration), global disease activity (according to the Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI-2K)[10] and damage (based on the Systemic Lupus International Collaborating Clinics/Damage Index)[11], histologic type of LN (according to the International Society of Nephrology/Renal Pathology Society classification)[12], elevated levels of anti-dsDNA antibodies and low complement C3/C4 levels, 24-h proteinuria, active urinary sediment (presence of casts and/or hematuria > 10 red blood cells per high power field), systolic and diastolic blood pressure (BP), diabetes and dyslipidemia (abnormal total cholesterol or triglycerides). Therapeutic variables included antimalarials, glucocorticosteroids (and dose), and immunosuppressives (azathioprine, mycophenolate mofetil, or cyclosporine). Variables that changed over time (from baseline to the end of followup) were also compared between groups in a time-dependent analysis.

Included individuals have provided written informed consent for studies being conducted at the UTLC and approved by the University Health Network Research Ethics Board (UHN/REB 11-0397).

Statistical analysis. Measurements of continuous variables are represented as mean ± SD, categorical variables as count (percent). Normality of continuous variables was assessed by plotting histograms. Comparisons were made using Wilcoxon rank-sum test or unpaired t tests for continuous and chi-square/exact chi-square tests for binary variables. Multivariable Cox regression analysis was performed for the identification of predictors for progression or transition to ESRD (baseline variables). Predictors associated with baseline CKD stages were not entered into the same regression model. A time-dependent multivariable Cox regression analysis was also performed for the identification of associated factors for progression (variables that changed over time). Step-down variable select method was used in the multivariable model building with Akaike information criterion used as an estimator of model fitting. Both multivariable analyses were adjusted for the decade of enrollment in the clinic. Statistical analysis was performed with SAS 9.4; $p < 0.05$ was considered significant.

RESULTS

Out of 700 patients with LN, 118 (16.86%) satisfied the inclusion criteria (74 with CKD 3b and 44 with CKD 4). The median time from LN (time of biopsy) to advanced CKD (second visit with an abnormal eGFR) was 5.6 years (range 0–34 years); 6.9 years for the CKD 3b patients and 3.9 years for the CKD 4 patients. Advanced CKD was evident in the first year after biopsy in 27/74 and 15/44 patients, respectively. There were no differences between groups (CKD 3b and CKD 4) at baseline regarding demographic, clinical, immunological, and therapeutic variables (details in Table 1). Similarly, there were no statistically significant differences in the histopathologic class of LN or the activity and chronicity indices.

Progression to ESRD occurred in 4 patients from the CKD 3b group (5.4%) and in an additional 25 patients from the CKD 4 group (56.8%; $p = 0.002$, Figure 1A). The overall incidence of ESRD was 4.3/100 patient-years. Transition from stage 3b to stage 4 occurred in another 16 patients (21.6%). Median time to stage change was 4.1 [interquartile range (IQR) 0.6–9.4] and 2.9 years (IQR 0.5–6.5) for the CKD 3b and CKD 4 groups, respectively (Figure 1B).

There were 45 "progressors" and 73 "non-progressors" who were followed for 5.8 ± 6.9 and 10.4 ± 8.0 years, respectively. Their baseline characteristics are shown in Table 2 (more details in Supplementary Table 1, available with the online version of this article). Patients who progressed were younger, had higher diastolic BP, and were taking glucocorticosteroids and antimalarials more frequently at baseline. They had proliferative LN (class III or IV) more frequently (66.7% vs 43.8%, $p = 0.033$) and the activity (5.7 ± 4.8 vs 4.5 ± 4.1, $p = 0.18$) and chronicity indices (3.1 ± 3.1 vs 2.1 ± 2.3, $p = 0.066$) were higher, although insignificantly. Their last median eGFR was 24.3 ml/min/1.73 m^2 (from 36 ml/min/1.73 m^2) for an average rate of decline of 2 ml/min/1.73 m^2 on an annual basis. On the contrary, the non-progressors did not lose any further renal function, with their last median eGFR being practically unaltered (37.1 ml/min/1.73 m^2 from 38.6 ml/min/1.73 m^2) and an annual decline of 0.14 ml/min/1.73 m^2. The overall decline in eGFR for progressors and non-progressors is shown in Figure 2.

Multivariate analysis for the identification of predictors for progression (using baseline variables) showed that active serology (positive anti-dsDNA antibodies plus low complements C3/C4) and CKD 4 stage at baseline were predictive of progression (Table 3). In a time-dependent model, considering the changes of the relevant variables over time, prednisone dose (for every increase of 1 mg/day) and CKD 4 were independently associated with progression. On the contrary, treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) was protective (Table 4).

DISCUSSION

In our present study, we showed that a substantial proportion (62%) of patients with LN-induced advanced CKD (eGFR = 15–44 ml/min/1.73 m^2) did not progress to a worse stage of kidney insufficiency or ESRD after an average followup of 10 years. This was particularly apparent for patients with CKD 3b, where only 5% progressed to dialysis. Active serology at the time of CKD (5.6 yrs after LN diagnosis on average) was strongly predictive of progression, implying that subclinical immune-mediated inflammation may still cause renal damage even years after the initial diagnosis.

Table 1. Baseline characteristics of the patients according to CKD severity.

Characteristics	CKD 3b, n = 74	CKD 4, n = 44	p
Age, yrs, mean ± SD	44.7 ± 13.4	40.8 ± 13.6	0.129
Female, % (n)	87.8 (65)	81.8 (36)	0.368
SLE duration, yrs, mean ± SD	12.3 ± 11.4	9.3 ± 6.7	0.116
Race/ethnicity, % (n)			0.35
White	67.6 (50)	56.8 (25)	
Black	17.6 (13)	15.9 (7)	
Chinese	4.1 (3)	11.4 (5)	
Other	10.8 (8)	15.9 (7)	
LN class, % (n)			0.655
II	27 (20)	20.5 (9)	
III	18.9 (14)	15.9 (7)	
IV	29.7 (22)	43.2 (19)	
V	16.2 (12)	15.9 (7)	
IV/V	2.7 (2)	0 (0)	
Activity index, mean ± SD	4.5 ± 4.1	5.8 ± 4.8	0.149
Chronicity index, mean ± SD	2.3 ± 2.6	2.8 ± 2.9	0.334
Creatinine, µmol/l, mean ± SD	149 ± 20	202 ± 56	< 0.001
eGFR, ml/min/1.73 m^2, mean ± SD	37.5 ± 5.5	24.4 ± 6.1	< 0.001
Proteinuria > 0.5 g/day, % (n)	58.1 (43)	54.5 (24)	0.558
Proteinuria, g/day, median (IQR)	1.1 (0.4–3.4)	1.0 (0.3–3.3)	0.952
Active urinary sediment, n (%)*	3 (4.1)	2 (4.5)	0.898
Anti-dsDNA+, % (n)	59.5 (44)	54.5 (24)	0.795
Low C3/C4, % (n)	48.6 (36)	50 (22)	0.887
Hb < 12 g/dl, % (n)	27 (20)	47.7 (21)	0.022
Systolic BP, mmHg, mean ± SD	137 ± 22	139 ± 24	0.51
Diastolic BP, mmHg, mean ± SD	84 ± 12	85 ± 12	0.635
Antihypertensives, % (n)	63.5 (47)	68.2 (30)	0.795
Treated with ACEI/ARB, % (n)	51.4 (38)	47.7 (21)	0.703
Diabetes, % (n)	12.2 (9)	13.6 (6)	0.725
Treated with statins, % (n)	24.3 (18)	20.5 (9)	0.628
Glucocorticosteroids, % (n)	82.4 (61)	86.4 (38)	0.574
Mean prednisone dose, mg/day, mean ± SD	21.9 ± 19.2	19.3 ± 17.0	0.495
Cumulative glucocorticosteroid dose, g, median**	16.4	16.6	0.796
Antimalarials, % (n)	39.2 (29)	36.4 (16)	0.76
Immunosuppressives, % (n)	51.4 (38)	63.6 (28)	0.194

* Casts and/or hematuria > 10 red blood cells per high power field. ** From LN diagnosis (time of biopsy) up to the baseline. CKD: chronic kidney disease; SLE: systemic lupus erythematosus; LN: lupus nephritis; eGFR: estimated glomerular filtration rate; IQR: interquartile range; Hb: hemoglobin; BP: blood pressure; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.

In a time-dependent analysis, prednisone dose was independently associated with progression (5% increased risk for every 1 mg increase of the daily prednisone dose) whereas treatment with ACE inhibitors/ARB was protective.

Several studies have investigated the factors that are associated with the development of ESRD in LN. The most common findings included the initial level of serum creatinine, the level of proteinuria, hypertension, and response to treatment[13–20]. More recent studies have also underlined the value of certain histopathologic characteristics that suggest chronic, irreversible damage[21]. However, the trajectory of the decline in renal function inevitably follows the transition from normal kidney function (eGFR > 90 ml/min/1.73 m^2) to CKD and subsequently, to ESRD. There is a lack of information concerning these intermediate stages of CKD in patients with SLE. Studies in the general population have shown significantly higher rates of progression in advanced CKD, albeit their cohorts were significantly older and comprised non-LN nephropathies. Baek, *et al* reported that 27.2% of the patients with CKD 3b did not progress in 10 years of followup[22], a number significantly lower than the 62% in our cohort. Hoefield, *et al* reported that about one-third of their referred CKD population (mean age 65 yrs, eGFR < 60 ml/min/1.73 m^2) died or required renal replacement therapy after a median followup of 26 months[23]. The incidence of renal replacement therapy was 5.1 events/100 patient-years, slightly higher than the 4.3 events/100 patient-years in our cohort.

Historically, the rate of renal function decline was believed to be linear and progressive once CKD is established[24]. However, studies have shown that the decline in renal function is characterized by episodes of acceleration and prolonged episodes of slower progression[25,26,27]. Li, *et al* showed that about 40% of the patients (mean age 56 yrs)

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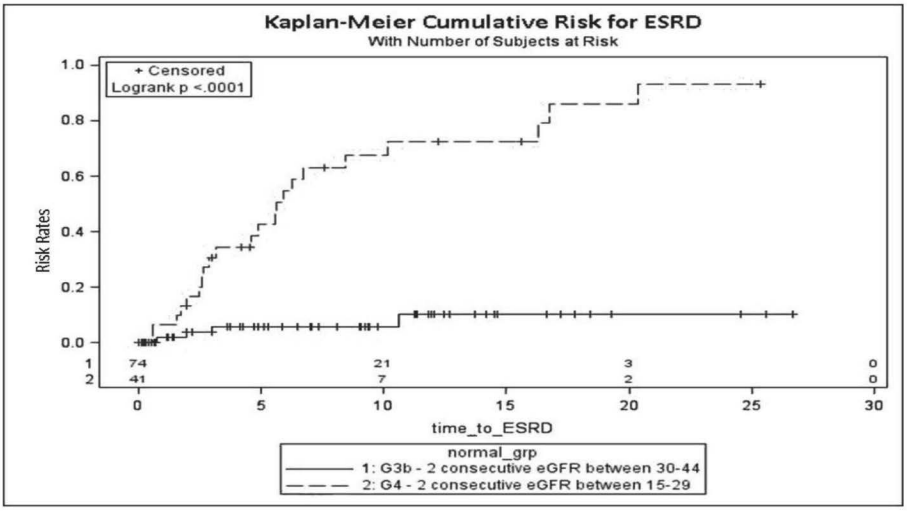

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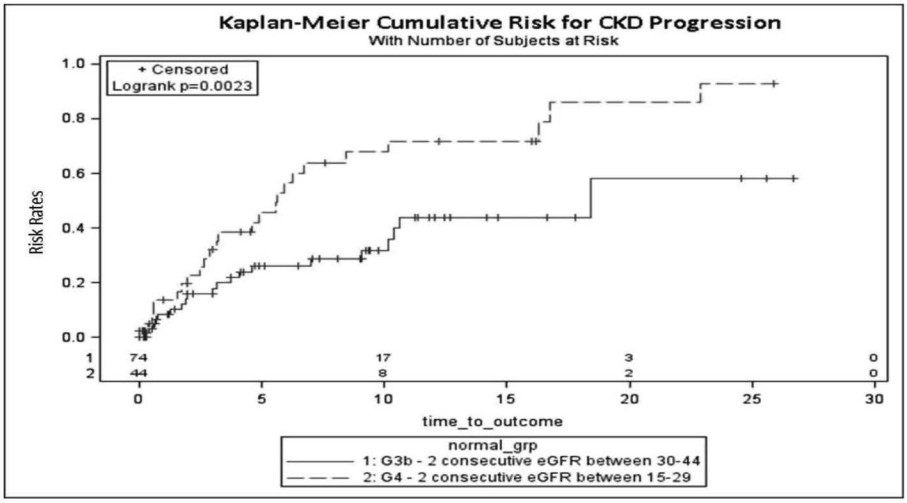

Figure 1. A. Kaplan-Meier curve depicting the progression to ESRD in the CKD 3b (solid line) and CKD 4 (dashed line) groups. B. Kaplan-Meier curve depicting the rate of progression to a worse stage of CKD for the 2 groups. ESRD: endstage renal disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; grp: group.

with CKD 3 would not progress over 9 years; progression was defined as an eGFR decline of more than 1 ml/min/1.73 m^2/year[27]. On the other hand, O'Hare, *et al* showed that a substantial proportion of patients who initiated dialysis had an accelerated decline in kidney function 2 years before dialysis[26]. About 25% of the patients had an annual GFR decrease of 15 ml/min/1.73 m^2, 9% had a decrease of 30 ml/min/1.73 m^2, while in 3% the kidney compromise was catastrophic, with progression from normal renal function to ESRD within 2 years. Heaf and Mortensen reported that about 62% of their patients had an accelerated loss of eGFR, which was significantly more common in CKD 4[25]. Patients who progressed to ESRD lost about 5.4 ml/min/1.73 m^2 during the last year before dialysis whereas individuals with hypertensive and diabetic nephropathy were losing 2.1 and 2.6 ml/min/1.73 m^2 annually[25]. In our cohort, the annual loss in eGFR was 2 ml/min/1.73 m^2 for the progressors.

In patients with LN, certain factors were identified to predict the progression to more severe CKD stages. Active serology at the time of CKD development (5.6 yrs after the renal biopsy) was strongly associated with progression. These results are in accordance with the findings of Dall'Era, *et al* from the longterm analysis of the Aspreva Lupus Management Study[28]. In that study, positive anti-dsDNA

Table 2. Baseline characteristics of the patients according to progression to a more severe CKD stage.

Characteristics	Progressors, n = 45	Non-progressors, n = 73	p
Age, yrs, mean ± SD	38.5 ± 11.9	46.2 ± 13.7	0.002
Females, % (n)	84.4 (38)	86.3 (63)	0.78
SLE duration, yrs, mean ± SD	10.7 ± 8.2	11.4 ± 11.0	0.703
White, % (n)	62.2 (28)	64.4 (47)	0.63
Blacks, % (n)	20 (9)	15.1 (11)	
Chinese, % (n)	8.9 (4)	5.5 (4)	
Others, % (n)	8.9 (4)	15.1 (11)	
LN class, % (n)			0.2
II	17.8 (8)	28.8 (21)	
III	20 (9)	16.4 (12)	
IV	46.7 (21)	27.4 (20)	
V	13.3 (6)	17.8 (13)	
IV/V	0 (0)	2.7 (2)	
Activity index, mean ± SD	5.7 ± 4.8	4.5 ± 4.1	0.18
Chronicity index, mean ± SD	3.1 ± 3.1	2.1 ± 2.3	0.066
SLEDAI-2K, mean ± SD	8.5 ± 5.7	7.6 ± 6.7	0.466
SDI, mean ± SD	1.7 ± 2.4	1.6 ± 1.9	0.866
Creatinine, µmol/l, mean ± SD	174 ± 41	165 ± 48	0.264
eGFR, ml/min/1.73 m^2, mean ± SD	34.7 ± 6.9	35.9 ± 7.8	0.393
Proteinuria > 0.5 g/day, % (n)	57.8 (26)	56.2 (41)	0.695
Proteinuria, g/day, median (IQR)	0.8 (0.3–3)	1.4 (0.4–3)	0.348
Active urinary sediment, % (n)*	6.7 (3)	2.7 (2)	0.304
Anti-dsDNA+, % (n)	66.7 (30)	52.1 (38)	0.129
Low C3/C4, % (n)	55.6 (25)	45.2 (33)	0.275
Anti-dsDNA + low C3/C4, % (n)	46.7 (21)	32.9 (24)	0.134
Hb < 12 g/dl, % (n)	46.7 (21)	27.4 (20)	0.033
Systolic BP, mmHg, mean ± SD	141 ± 22	136 ± 23	0.237
Diastolic BP, mmHg, mean ± SD	87 ± 10	82 ± 12	0.014
Antihypertensives, % (n)	68.9 (31)	63.0 (46)	0.4
Treated with ACEI/ARB, % (n)	53.3 (24)	47.9 (35)	0.57
Diabetes, % (n)	11.1 (5)	13.7 (10)	0.667
Treated with statins, % (n)	17.8 (8)	26.0 (19)	0.3
Glucocorticosteroids, % (n)	93.3 (42)	78.1 (57)	0.029
Mean prednisone dose, mg/day, mean ± SD	19.9 ± 19.3	16.1 ± 17.9	0.273
Cumulative glucocorticosteroid dose, g, mean ± SD**	21.3 ± 27.4	18.7 ± 32.9	0.651
Antimalarials, % (n)	51.1 (23)	30.1 (22)	0.023
Years on antimalarials, mean ± SD**	0.2 ± 5.8	1.4 ± 5.1	0.222
Immunosuppressives, % (n)	60.0 (27)	53.4 (39)	0.485
Years taking immunosuppressives, mean ± SD**	2.1 ± 9.1	1.9 ± 6.0	0.886

* Casts and/or hematuria > 10 red blood cells per high power field. ** From LN diagnosis (time of biopsy) up to the baseline. CKD: chronic kidney disease; SLE: systemic lupus erythematosus; LN: lupus nephritis; eGFR: estimated glomerular filtration rate; IQR: interquartile range; Hb: hemoglobin; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; BP: blood pressure; ACEI: angiotensin- converting enzyme inhibitors; ARB: angiotensin receptor blockers.

antibodies at the end of the induction phase were associated with an 8-fold increased risk of treatment failure (a composite of either death or ESRD or doubling of serum creatinine or renal flare or requirement for rescue therapy). In the same study, failure to restore normal complement levels at Week 8 after initiation of therapy was marginally associated with treatment failure. The persistence of anti-dsDNA positivity and/or low C3/C4 levels may imply an ongoing immune complex–mediated tissue damage even in the absence of clinically evident activity (without active urinary sediment or massive proteinuria). About one-third of our patients who did not progress had active serology at the time of CKD diagnosis, suggesting that these patients may still benefit from immunosuppressive treatment and could be considered for clinical trials.

The role of inflammation in CKD progression has been also shown in 3440 non-SLE patients in the Chronic Renal Insufficiency Cohort study[29]. Elevated serum levels of fibrinogen, interleukin (IL) 6, tumor necrosis factor (TNF)-α, and low serum albumin were associated with rapid loss of kidney function (defined as a > 50% loss of eGFR, or ESRD). IL-6 and TNF-α are implicated in the pathogenesis of LN[30], while low serum albumin may reflect the severity of proteinuria and thus, the extent of the basement membrane damage.

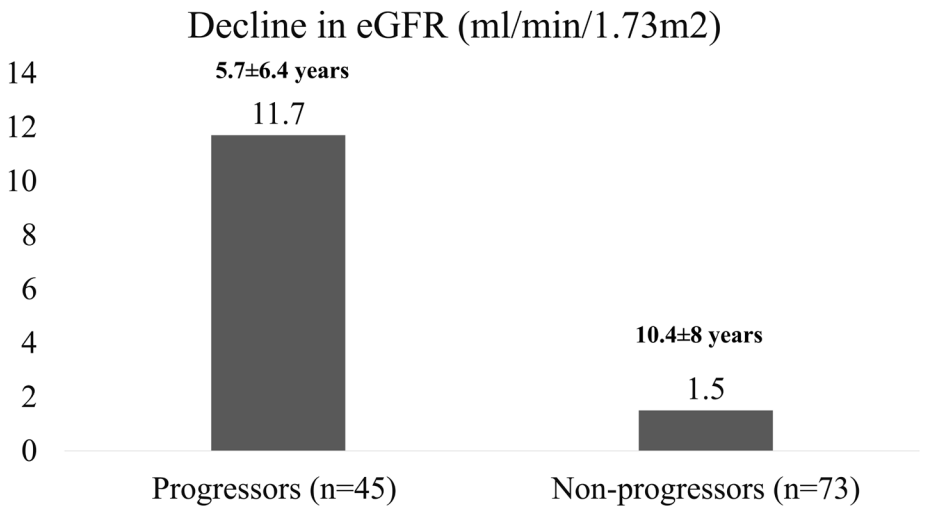

Figure 2. Overall decline in eGFR (median difference from baseline to the last visit or initiation of dialysis) for progressors and non-progressors. eGFR: estimated glomerular filtration rate.

Table 3. Predictors (variables present at baseline) for progression of CKD.

Variables	HR	Lower 95% CI	Higher 95% CI	p
Univariate analysis				
Age	0.967	0.943	0.991	0.007
Proliferative LN (III + IV)	2.223	1.192	4.145	0.012
SLEDAI-2K	1.049	1.003	1.098	0.038
eGFR	0.929	0.898	0.962	< 0.001
Anti-dsDNA + low C3/C4	2.926	1.603	5.34	< 0.001
Hb < 12g/l	2.334	1.264	4.309	0.007
Antimalarial treatment	1.98	1.089	3.601	0.025
CKD 4 (compared to CKD 3b)	2.487	1.379	4.486	0.003
Multivariate analysis				
Anti-dsDNA + low C3/C4	2.72	1.41	5.24	0.003
CKD 4 (compared to CKD 3b)	2.76	1.5	5.08	0.001

CKD: chronic kidney disease; LN: lupus nephritis; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; eGFR: estimated glomerular filtration rate; Hb: hemoglobin.

Table 4. Factors associated with progression of CKD (time-dependent multivariate analysis).

Variables	HR	Lower 95% CI	Higher 95% CI	p
Simple time-dependent Cox regression (univariate)				
SLEDAI-2K	1.08	1.02	1.15	0.011
Anemia (Hb < 12 g/l)	2.07	1.11	3.87	0.023
Systolic BP	1.02	1.001	1.035	0.038
Prednisone dose (for 1 mg/day increase)	1.033	1.015	1.051	0.0003
CKD 4 (compared to CKD 3b)	2.458	1.34	4.51	0.004
Multivariate time-dependent Cox regression				
Prednisone dose (for 1 mg/day increase)	1.05	1.03	1.07	< 0.0001
CKD 4 (compared to CKD 3b)	2.95	1.53	5.69	0.001
Treatment with ACEI/ARB	0.39	0.2	0.77	0.007

CKD: chronic kidney disease; Hb: hemoglobin; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; Hb: hemoglobin; BP: blood pressure; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.

In a time-dependent analysis, an increase in the daily prednisone dose by 1 mg was associated with a 5% risk of progression in CKD. This finding reflects relapsing or refractory disease after several years from LN diagnosis and coincides with previous reports regarding the effect of treatment failure on progression[13-20]. On the other hand, treatment with ACE inhibitors/ARB was protective against progression (61% less risk with continuous therapy). The nephroprotective properties of these drugs are well established in diabetic nephropathy as well as other types of proteinuric nephropathies[31,32]. To our knowledge, this is the first study to provide such information on LN and to confirm the value of ACE inhibitors/ARB treatment even in advanced CKD.

The protective effects of ACE inhibitors/ARB are many and probably extend beyond BP control and proteinuria. In our present study, most patients (56.8%) had proteinuria > 0.5 g/day (the current threshold for SLEDAI-2K) with a median of 1 g/day whereas only 4.2% had active urinary sediment (casts and/or hematuria). However, proteinuria does not necessarily reflect disease activity in such cases. Hoefield, *et al* reported that the mean proteinuria of their patients (non-SLE CKD) was 0.87 g/day for CKD 3b (n = 431) and 1.08 g/day for CKD 4 (n = 481)[23], while that was increased to 2.23 g/day in 175 patients with eGFR < 15 ml/min/1.73 m^2. In the non-SLE CKD patients, this is commonly attributed to glomerulosclerosis with limited reversibility. In LN-related CKD, however, only renal biopsy would offer significant diagnostic assistance. It has been shown that 53% of the 686 patients with refractory or recurrent LN had a histologic transformation within 5 years since the first renal biopsy[33]. This led to a change in immunosuppressive therapy in 57% (no changes in 43%) with intensification in 39% and tapering in 18% of the patients. Of note, the chronicity index was increased between biopsies in 83% of the patients, while the activity index was decreased in 97%[33]. The reasons for repeated biopsy in that study included worsening proteinuria and nephrotic syndrome along with increasing serum creatinine and progression to renal failure. Data only on the latter (solely increased serum creatinine) were not provided and longterm outcomes (e.g., renal survival) were not discussed.

Limitations of our present study include its observational character. Details of the initial treatment for LN are not known for all individuals because many were enrolled in late stages of the disease when they already had CKD. Patients' compliance to therapy was also unknown. Individuals were not followed for the same length of time, and disease management (immunosuppressives, antihypertensives, etc.) after CKD diagnosis was not standardized. However, to our knowledge this is the first study to assess the progression of advanced LN-related CKD in a prospectively followed cohort within a single center.

About 62% of our patients with LN-related CKD did not progress to ESRD or to a worse stage of renal insufficiency after 10 years of followup on average. That was particularly apparent in patients in CKD 3b because only 5% of them developed ESRD. The annual rate of renal function decline was similar to that of hypertensive nephropathy for the patients who progressed (about 2 ml/min/1.73 m^2), while that was negligible (0.14 ml/min/1.73 m^2) in the non-progressors. Active serology (increased anti-dsDNA antibodies and low complements C3/C4) at the time of CKD development were predictive of progression. Any increase in prednisone dose after that time was associated with progression, while therapy with ACE inhibitors/ARB was related to a lesser likelihood of progression. Dialysis is not inevitable in LN-related advanced CKD.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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