Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus

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Advances in immunotherapy have improved survival of patients with systemic lupus erythematosus who now face an increasing burden of chronic diseases including that of the kidney. As systemic inflammation is also thought to contribute directly to the progression of chronic kidney disease (CKD), we assessed this risk in patients with lupus, with and without a diagnosis of nephritis, and also identified modifiable risk factors. Accordingly, we enrolled 631 patients (predominantly Caucasian), of whom 504 were diagnosed with lupus within the first year and followed for an average of 11 years. Despite the presence of a chronic inflammatory disease, the rate of decline in renal function of 238 patients without nephritis was similar to that described for non-lupus patient cohorts. Progressive loss of kidney function developed exclusively in patients with lupus nephritis who had persistent proteinuria and dyslipidemia, although only six required dialysis or transplantation. The mortality rate was 16% with half of the deaths attributable to sepsis or cancer. Thus, despite the presence of a systemic inflammatory disease, the risk of progressive CKD in this lupus cohort was relatively low in the absence of nephritis. Hence, as in idiopathic glomerular disease, persistent proteinuria and dyslipidemia (modifiable risks) are the major factors for CKD progression in lupus patients with renal involvement.

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The focus of care of patients with systemic lupus erythematosus (SLE) has traditionally emphasized control of life-threatening disease flares, and less attention has been paid to the potential burden of chronic kidney disease (CKD). Recognized as a global public health problem, CKD is associated with a high risk of mortality, end-stage renal disease, and cardiovascular disease; prevention of progressive CKD is therefore a priority.[1] Emerging research suggests that systemic inflammation contributes directly and indirectly to progressive CKD.[2–4] This paradigm would suggest that patients with a systemic inflammatory disease such as SLE face a risk of progressive CKD, even in the absence of specific autoimmune kidney involvement (that is, nephritis). Impaired renal function is not only a risk factor for end-stage renal disease but CKD may also contribute to the high cardiovascular risk observed in patients with SLE.[5–11]

The long-term course of renal function in patients with SLE without autoimmune kidney involvement (according to the American College of Rheumatology (ACR) criteria[12]) is not well described; however, given the prevailing hypothesis linking inflammation and CKD, it is plausible that this is a vulnerable population. In addition to the presence of systemic inflammation, medication toxicity (drug-related hypertension and metabolic abnormalities, use of nephrotoxic non-steroidal anti-inflammatories) may also contribute to CKD in this population. With respect to patients with known lupus nephritis, available data suggest wide variation in long-term clinical outcome of patients who have SLE nephritis.[13–20] It is also important to define the rate of kidney function decline in patients with renal autoimmune involvement to help clinicians balance the risks of immunosuppressive drugs with the risk of progressive CKD.

Accordingly, we have studied the course of long-term kidney function in a large predominantly Caucasian inception cohort of prospectively followed up subjects with SLE (with and without known renal involvement), in an effort to better understand the long-term course of kidney function in

these individuals. We determined the proportion of patients who develop CKD according to the KDIGO (Kidney Disease: Improving Global Outcomes) [21] definitions to contextualize their loss of kidney function and characterize the risk of CKD according to internationally accepted guidelines. Recognizing that this definition may not reflect CKD that is likely to evolve into advanced renal insufficiency, we also identified whether the CKD was progressive in nature by studying the rate of renal function decline over time. Finally, we related clinical parameters to the rate of renal function decline to maximize our ability to refine therapeutic goals to prevent loss of kidney function.

RESULTS

Characteristics of inception cohort

This was a predominantly female (87%) Caucasian (77%) cohort; the balance was African Caribbean (9.4%) or Chinese (7%). The mean body mass index at the time of enrollment was $27.4 \pm 8.1\,kg/m^2$. Only 9 subjects (1.8%) were diabetic, and 109 subjects (22%) smoked at baseline.

During 11 years of follow-up, half of the subjects (53%) developed evidence of renal involvement of SLE according to the ACR criteria.[12] An additional 35 subjects developed diabetes during the course of follow-up; a total of 8.7% ever had diabetes.

Development of progressive and non-progressive CKD

In total, 18% of the population had CKD at the time of last follow-up (Table 1). Of patients who never had ACR-defined renal lupus, only a small group had evidence of CKD ($n = 28$) according to the KDIGO criteria at the time of last follow-up. These patients were older (54 years) and had renal insufficiency at the time of enrollment, but had a low rate of renal function decline over time (-0.662 ml/min per $1.73\,m^2$ per year), suggesting that these patients have non-progressive CKD. Of patients who did have ACR-defined renal lupus, 63/266 (24%) had CKD at last follow-up. Although these subjects also had impaired renal function at the time of enrollment, they were younger (39 years) and their rate of renal function decline was -4.35 ml/min per $1.73\,m^2$ per year, suggesting a progressive course. Only six patients developed end-stage renal disease requiring long-term dialysis or transplantation; all had renal lupus nephritis.

Although the adjusted mean SLE disease activity index (SLEDAI) (AMS) score across the four groups differed, the non-renal-adjusted mean SLEDAI did not and the difference in AMS was mostly related to the presence of renal disease activity parameters. In addition, measures of c-reactive protein (CRP) did not differ across groups, although there was a trend toward a higher level in the group of older individuals with non-progressive CKD without nephritis ($P > 0.05$). Patients with CKD, according to the KDIGO definition, had higher cholesterol, sustained time-averaged (TA) mean arterial pressure (MAP), and sustained TA proteinuria.

During the course of their follow-up, 35 patients developed diabetes (9 patients had diabetes at the time of enrollment). The proportion of patients with diabetes diagnosed either at inception or during follow-up did differ across groups (Table 1), and the impact of this on kidney function decline is described below. There was no difference in the proportion of patients who smoked (33%) at the time of enrollment or during the course of follow-up across groups.

Predictors of progressive CKD

To better understand predictors of the rate of kidney function loss, clinical variables were related to the rate of renal function decline as previously described.[22–27] The mean rate of renal function decline or slope of estimated glomerular

Table 1 | Characteristics of patients according to whether they ever had lupus renal involvement (by the ACR criteria) and development of CKD

	Full cohort (*N*=504)	Never renal involvement, no CKD (*N*=210)	Never renal involvement, CKD at last follow-up (*N*=28)	Renal involvement, no CKD (*N*=203)	Renal involvement, CKD at last follow-up (*N*=63)
Age at enrollment (years)	35 ± 14	35 ± 12	54 ± 14	33 ± 12	39 ± 17
Duration of follow-up (years)	11.3 ± 8.3	9.6 ± 7.4	11.6 ± 8.3	12.6 ± 8.8	12.7 ± 8.5
eGFR at enrollment (ml/min per $1.73\,m^2$)*	89 ± 29	95 ± 22	63 ± 20	94 ± 29	64 ± 34
Rate of renal function decline* (ml/min per $1.73\,m^2$ per year)	−1.513 ± 7.1	−1.255 ± 6.0	−0.662 ± 3.1	−1.018 ± 6.3	−4.35 ± 11.9
Adjusted mean SLEDAI	5.1 ± 3.4	4.4 ± 2.9	3.6 ± 2.2	5.4 ± 3.4 (non-renal 3.7 ± 2.8)	7.2 ± 4.2 (non-renal 4.2 ± 2.2)
Average CRP/hsCRP	6.03/4.2	5.0/3.4	12.3/9.5	6.3/4.4	6.5/5.0
TA cholesterol*	5.1 ± 1.11	4.8 ± 0.8	5.3 ± 1.0	5.1 ± 1.1	6.1 ± 1.5
TA MAP* (mm Hg)	93.0 ± 9.4	89.9 ± 8.3	99.7 ± 7.5	92.5 ± 8.4	102.1 ± 8.4
TA proteinuria* (g/day) med (min, max)	0.71 (0, 10)	0.09 (0, 0.45)	0.11 (0.05, 0.45)	0.35 (0, 6.2)	1.1 (0.06, 10)
Diabetes, *N* (%)*	44 (8.7)	10 (4.8)	0	24 (11.8)	10 (15.9)
Deceased at last follow-up* (%)	73 (14.5)	14 (6.7)	6 (21)	29 (14)	24 (38)

Abbreviations: ACR, American College of Rheumatology; ANOVA, analysis of variance; CKD, chronic kidney disease; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity CRP; MAP, mean arterial pressure; SLEDAI, systemic lupus erythematosus disease activity index; TA, time-averaged.
Values are mean ± s.d., unless otherwise indicated. Variables with statistically significant differences across groups are indicated by * (*$P < 0.05$ for ANOVA).

Table 2 | Factors predictive of the rate of renal function decline

Variable	Univariate regression		Multivariate regression	
	Unadjusted β-coefficient ± s.e.	*P*-value	β-Coefficient ± s.e.	*P*-value
Age at inception	0.059 ± 0.022	0.01	−0.03 ± 0.03	0.46
eGFR at inception	−0.077 ± 0.010	<0.001	−0.094 ± 0.013	<0.0001
MAP at inception	0.05 ± 0.02	0.1	0.04 ± 0.03	0.2
TA proteinuria	−0.965 ± 0.292	<0.001	3.5 ± 1.4	0.02
Mean average cholesterol	−1.320 ± 0.276	<0.001	−1.25 ± 0.4	<0.0001
Interaction term (proteinuria × cholesterol)	See text		−0.55 ± 0.20	0.009
Adjusted mean SLEDAI with renal components	−0.314 ± 0.092	<0.001	−0.28 ± 0.11	0.03
Number of renal SLE flares	−0.561 ± 0.189	0.003	−0.5 ± 0.23	0.25

Abbreviations: eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; TA, time-averaged.
Results of univariate and multivariate linear regression analyses. The β-coefficients provided are derived from the full multivariate model.

filtration rate (eGFR) of all subjects was −1.5 ml ± 7.1 ml/min per 1.73 m^2 per year. The age at first presentation, eGFR at presentation, TA sustained proteinuria, TA cholesterol, adjusted mean SLEDAI score (including renal components), number of renal flares, and MAP at inception were predictive of the rate of progression of renal function decline by univariate linear regression analysis (Table 2). There was a statistically important interaction between cholesterol and proteinuria.

By univariate analysis, it was determined that several variables were not related to the rate of renal function decline. Slope did not differ according to smoking status or race. Although more patients with lupus nephritis and CKD developed diabetes during the course of follow-up, diabetes was not associated with a more rapid rate of renal function decline. The adjusted mean non-renal SLEDAI was not predictive of slope, nor were the average CRP or high-sensitivity CRP values. The body mass index, 24-h urine protein, anti-ds-DNA, and C3 titers at the time of first presentation were not predictive of the slope, nor was the TA MAP; these variables were therefore not considered in the multivariate model. There were too few male subjects to detect effects of gender on the rate of renal function decline. The rate of renal function decline did not differ between subjects whether they did or did not receive ACE inhibitors or angiotensin receptor blockers.

When the multivariate model was analyzed, age and baseline MAP no longer remained a significant predictor of slope. However, the baseline renal function at the time of presentation, TA proteinuria, TA cholesterol, and adjusted mean SLEDAI score (with renal components) remained significant independent predictors of the rate of renal function decline (adjusted R^2 for the multivariate model is 0.245, $P<0.0001$).

Impact of sustained proteinuria on progression

The rate of renal function decline differed significantly according to the level of TA proteinuria (Table 3, $P<0.05$ adjusted for unequal variance). The slope was 6–7 times greater in subjects with over 2 g/day of TA proteinuria compared with subjects with under 2 g/day of proteinuria (adjusted *P*-values <0.05).

Table 3 | Rate of renal function decline according to category of TA proteinuria

TA urine protein excretion (g/day)*	Number of subjects	Slope of eGFR (ml/min per 1.73 m^2 per year)
0–1	275	−1.15 ± 5.37
1–2	32	0.32 ± 8.98
>2	36	−6.68 ± 14.6

Abbreviations: eGFR, estimated glomerular filtration rate; TA, time-averaged.
*$P<0.05$ comparing slope across categories of TA proteinuria.

Table 4 | Clinical characteristics of subjects with biopsy-proven WHO class III, IV, or V SLE nephritis, and the rate of renal function decline according to remission status

Baseline (n=98)	
Number with only class V lesion	16
Baseline eGFR (ml/min per 1.73 m^2)	81.08 ± 30.6
Median baseline proteinuria (range) (g/24 h)	1.00 (0.2–36)
Duration of follow-up (years)	12.36 ± 8.4
Follow-up	Slope (ml/min per 1.73 m^2 per year) ± s.d.
All subjects	−1.38 ± 6.8
Complete remission, *n*=73	−0.429 ± 6.34
Partial remission, *n*=9	−0.058 ± 5.87
No remission, *n*=16	−6.49 ± 7.33

Abbreviations: eGFR, estimated glomerular filtration rate; SLE, systemic lupus erythematosus.

Impact of resolution of renal flares on progression and survival

Although many patients had renal SLE involvement according to the ACR criteria, 98 subjects had biopsy-proven, WHO or ISN-RPS class III, IV, or V lupus nephritis (Table 4). Subjects who did not reach a complete or partial remission of their nephritis flare had a rate of renal function decline that was 30 times faster than that of subjects who did ($P<0.05$).

CKD and cohort mortality

At the time of last follow-up, 15% of subjects had died (Table 1). The rate of renal function decline was significantly related to the risk of death; when accounting for renal function at the time of inception, for every 1 ml/min per 1.73 m^2 faster rate of GFR loss per year, there was a 1.15-fold increased risk of death (95% confidence interval for hazard ratio 1.11–1.19, $P<0.0001$). The primary cause of death

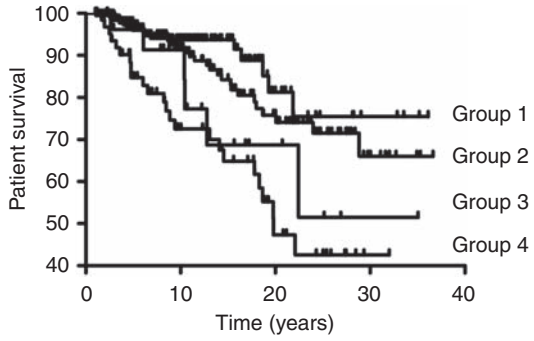

Figure 1 | Survival from the time of inception, according to whether subjects ever had lupus renal involvement (by the American College of Rheumatology (ACR) criteria) and development of CKD at last follow-up. Group 1: no renal involvement of lupus, no CKD; Group 2: no renal involvement of lupus but did develop CKD; Group 3: renal involvement of lupus but no CKD; Group 4: renal involvement of lupus and CKD at last follow-up.

(ICD-9 code) was available for 84% of the deceased; half of the coded deaths were attributable to cancer or sepsis, and the remainder was mostly due to cardiovascular disease. The patient mortality during follow-up is illustrated in Figure 1. This figure is provided for descriptive purposes, as the survival time would be highly correlated with the time to development of CKD.

In the 98 patients with biopsy-proven lupus nephritis, mortality risk was evaluated using survival analysis; survival was calculated from the time of first biopsy evidence of class III, IV, or V nephritis. The risk of mortality in this subgroup was not related to renal function at the time of biopsy, but was independently related to sustained proteinuria and MAP during the 2 years of follow-up following biopsy.

DISCUSSION

We studied a large, primarily Caucasian inception cohort of subjects with and without renal SLE involvement to describe the burden of CKD in this population and identify risk factors associated with progressive renal function decline.

Our first finding was that two distinct groups of patients with SLE develop CKD during long-term follow-up. The first group includes individuals diagnosed with SLE at an older age who do not have documented ACR-defined autoimmune renal involvement. The second group comprises individuals with renal lupus who have sustained proteinuria and dyslipidemia. Given the important contribution of age and baseline renal function to the KDIGO definition of CKD used in this study, the rate of renal function decline in these patients is an important indicator as to whether this represents stable or progressive CKD. The subgroup of patients with 'CKD' who were older at the time of diagnosis ($n = 28$) had minimal renal function decline during the period of follow-up (-0.662 ± 3.1 ml/min per $1.73\,m^2$ per year), which is comparable to that observed in healthy populations.[28–30]

The relatively low rate of renal function decline observed in our cohort as a whole is surprising,[11,15,31] given the prevailing theory that systemic inflammation contributes directly to kidney injury and progressive CKD,[2–4] potentially by precipitating microvascular injury. SLE is regarded as a prototype of systemic inflammatory conditions, and this systemic inflammation is thought to contribute to the elevated risk of cardiovascular events in this population;[32] however, this has not previously been extended to the study of loss of kidney function in patients with SLE who do not have documented autoimmune renal involvement. The incremental risk of kidney failure is likely small if one projects this rate of renal function declines to 30 years of follow-up. One possible explanation for this observation is that the majority of the population consists of premenopausal women, and the protective effects of estrogen during the observation period may in part counterbalance the effects of systemic inflammation on the vasculature,[33] unless patients have severe or poorly responsive autoimmune renal disease. Another possible factor affecting CKD risk in this population is the competing risk of death, which considers that premature mortality prevents the development of CKD. Finally, it may be that the inflammatory aspect of lupus was not as prominent in this cohort; patients without SLE-related nephritis had relatively low adjusted mean SLEDAI scores, reflecting low average levels of disease activity over the period of follow-up.

Our second finding is that in the cohort of patients with lupus nephritis, both TA proteinuria and cholesterol are important interrelated and modifiable risk factors for progressive loss of kidney function. This approach relating TA variables to the rate of kidney function decline (eGFR slope) in patients with SLE builds upon previous work indicating that, in the shorter term, proteinuria is a predictor of doubling of serum creatinine and kidney failure in patients with SLE nephritis.[11] This approach also permits finer resolution in terms of proteinuria targets for long-term preservation of kidney function in patients with SLE. Although sustained proteinuria is recognized as the most important predictor of the rate of renal function decline in primary glomerulonephritis,[24–26] this has not been as extensively explored in patients with secondary forms of glomerular disease. Similar to subjects with immunoglobulin A nephropathy,[26] incremental degrees of sustained TA proteinuria in our SLE cohort were associated with a more rapid rate of renal function decline: up to sevenfold greater in subjects with >2 g/day of TA proteinuria. Furthermore, we found that subjects who have sustained proteinuria following biopsy-proven class III, IV, or V nephritis have a 30-fold greater rate of renal function decline compared with those who achieve a complete or partial remission of their proteinuria. Whether this sustained proteinuria represents residual untreated renal inflammation,[34] scarring, or systemic inflammation is not known. Although these findings highlight the clinical importance of sustained proteinuria, they also emphasize the need for careful assessment of risk and

benefit of therapy. Half of the mortality observed in patients was attributable to sepsis or cancer; although these deaths may be related to renal disease, it is equally plausible that they relate to complications of intensified immunosuppression.

Several study limitations require discussion. First, the renal outcomes of our cohort, even those with renal SLE involvement, were more favorable than previously reported in other populations of patients with lupus nephritis.[11,15] One possible explanation is the racial composition of our cohort, which was predominantly Caucasian. Indeed, race is an important predictor of outcome of lupus nephritis, and wide variations in short- and long-term renal outcome have been described,[15,35,36] with particularly poor outcomes in patients of African and Caribbean descent. Although we did not observe differences in outcome according to race, our study may have had insufficient representation of vulnerable groups of interest. In addition, the impact of differences in socioeconomic status was not studied in this cohort of patients with universal health-care access. Next, we used a linear model to measure the rate of renal function decline (slope) to identify risk factors for progressive renal impairment. Slope-based studies use individually observed change in renal function over time as the outcome of interest[37] to identify risk factors for loss of renal function,[38] or impact of interventions [39] in CKD, and these analyses rely on the assumption that loss of renal function is linear over time.[40–42] Although SLE is characterized by flares of disease activity, we hypothesized that, in addition to flares of both renal and extrarenal inflammatory disease activity, ongoing proteinuria, hypertension, and dyslipidemia contribute to progressive renal function decline in subjects with SLE. It is possible that nonlinear techniques to model renal function decline may have identified additional predictors of CKD. Another consideration with slope-based analyses is that some of the covariates may be dependent upon the duration of follow-up (for example, number of renal flares), which in this analysis was not fixed. However, using this approach has allowed us to contextualize the course of lupus-related kidney disease in relation to that of patients with idiopathic forms of kidney disease,[24–26] and the findings with respect to predictors of renal deterioration are surprisingly similar. Finally, as this is not a randomized study, the relationship between treatment and outcome in this study is primarily descriptive; the impact of specific interventions on the risk of CKD was beyond the scope of this study.

In summary, despite exposure to a milieu of systemic inflammatory disease, the risk of progressive CKD in patients with SLE is low; progressive CKD occurs primarily in individuals who have autoimmune renal involvement with persistent sustained proteinuria and dyslipidemia. The rate of renal function decline in the remainder of the cohort is comparable to that described in the general population, and the clinical impact on risk of end-stage kidney disease is likely modest. Although the favorable renal outcome may reflect aggressive immunosuppressive regimens, the high rate of non-renal mortality emphasizes the need for ongoing trials to define the goals of maintenance immunosuppressive treatment, to help balance risks of treatment with prevention of progressive CKD.

MATERIALS AND METHODS

Subjects

Since 1970, the University of Toronto Lupus Clinic (UTLC) has prospectively followed up patients with a confirmed diagnosis of SLE[43] (that is, those fulfilling four of the 1971 or 1982 ACR classification criteria[12] or three ACR criteria plus having a diagnostic histologic lesion of SLE on renal or skin biopsy). Patients are followed up according to a standard protocol in a manner consistent with the principles of the Declaration of Helsinki. For each patient, a complete history, physical examination, and laboratory values are recorded at entry and at intervals of 2–4 months, with the exception of certain laboratory tests, such as serum lipid concentrations, which are carried out annually.

Data were obtained from an inception cohort of 631 subjects entered into the UTLC within 1 year of diagnosis of SLE, who were followed up in the UTLC up to March 2008. Of the 631 subjects, 116 were excluded because they had <1 year of follow-up, and 11 were excluded because they had measures of creatinine <3. Data from 504 subjects were available for analysis; at the time of final analysis, 30% were lost to follow-up; available data were included in the analysis but censored at their last visit.

Rate of renal function decline—slope

Given that the development of CKD may depend upon the duration of follow-up, predictors of progressive CKD were studied in relation to the rate of renal function decline, as previously described.[22–27] The rate of renal function decline was expressed as the slope of eGFR (calculated by MDRD (Modification of Diet in Renal Disease Study) formula[44,45]) obtained by fitting a straight line through the calculated eGFR values using linear regression and the principle of least squares. This was plotted and visually examined for each patient. As previously described, outlier measurements (that is, eGFR of $\geqslant 40\%$ within a 3-month time frame not sustained or associated with changes in immunotherapy) were removed from the calculation;[24–27] this was carried out in less than 10 curves. CKD was defined according to the KDIGO guidelines,[21,46] as a sustained eGFR $\leqslant 60$ ml/min/1.73 m^2.

Clinical parameters

MAP. For each patient, an average MAP was determined for each 6-month block during follow-up; the average of MAP for every 6-month period is represented by the time-average (TA) MAP.

Proteinuria. Similar to the TA MAP, the TA proteinuria represents an average of the mean of 24-h proteinuria measurements for every 6-month period. For example, if a patient had three measurements in a 6-month block and four measurements in the subsequent 6-month block, a mean value was obtained for each of the 6-month blocks, and the TA proteinuria is derived from the average of these two values.

Cholesterol. In a similar manner to MAP and proteinuria, an average mean cholesterol measurement was calculated for every patient.

CRP. CRP was serially and prospectively measured on registry patients from September 2000 to 2003. This was subsequently replaced by the high-sensitivity CRP assay. Average mean CRP and

high-sensitivity CRP values were calculated for every patient according to assay results available for analysis.

Assessment of SLE disease activity. This was based on the SLEDAI-2K, recorded prospectively at predetermined intervals in the database.[47] An adjusted mean SLEDAI score (AMS) was calculated for each patient and describes disease activity over time. It is equivalent to the area under the curve of SLEDAI-2K over time divided by time interval.[48] To isolate the non-renal components of the SLEDAI score, the renal components were removed from the calculated SLEDAI, and an adjusted mean non-renal SLEDAI was calculated in a similar manner.

Assessment of remission status. Although half of patients had renal involvement according to ACR criteria, 98 had biopsy-proven class III, IV, or V nephritis. We studied the impact of remission status in this subgroup. Remission status following a renal flare was defined as per Chen *et al.*[49] Complete remission was defined as attainment of a serum creatinine level $\leqslant 120\,\mu mol/l$ (1.4 mg/dl) and 24-h urine protein excretion <0.3 g/day or negative by dipstick at any time following the initial flare. Partial remission was defined as a serum creatinine level that returned to within 25% of baseline before the flare, and a $\geqslant 50\%$ reduction in proteinuria to under 1.0 g/day ($\leqslant 0.3$ g/l by dipstick). All other patients who had a flare but did not meet the criteria of complete or partial remission at any time following their biopsy were considered to have no remission.

Statistical analysis

Data were analyzed using SAS (version 9.1, SAS Institute, Cary, NC). For descriptive statistics, normally distributed variables are expressed as mean ± s.d. and compared using *t*-test or analysis of variance as required, accounting for unequal variance as required. Variables with a skewed distribution or non-parametric variables are expressed as median and range, and were compared using the Mann–Whitney *U*-test. Categorical associations were compared using Fisher's exact test. A two-tailed $P<0.05$ was considered statistically significant.

For determining statistical associations with kidney function decline, given that the development of CKD depends upon the duration of follow-up, and that CKD may not be progressive, clinical TA variables were studied in relation to the rate of renal function decline in the full inception cohort population, as previously described.[22–27] For multivariate analysis, only variables significantly associated with slope by univariate analysis, at a threshold *P*-value of 0.1, were included in the multivariate model to determine independent predictors of slope. The effect of renal SLE flares on rate of renal function decline was considered as both a continuous variable (number of flares, Table 2) and a dichotomous variable (flare yes/no). As proteinuria distribution was skewed (at presentation and time averaged), natural log-transformed values were used in the regression analysis, and similar results in terms of the significance of proteinuria were obtained with non-transformed data (not shown). Multivariate regression models were assessed by stepwise and block entry of variables. Similarly, when studying the group of patients with biopsy-proven class III, IV, or V nephritis, the rate of renal function decline was compared across remission categories.

For analyses relating to patient mortality, Kaplan–Meier survival curves were generated using GraphPad Prism (version 4, GraphPad Software, La Jolla, CA) (Figure 1). Given that the development of CKD is dependent upon time of follow-up, this figure was constructed for descriptive purposes, but statistical comparisons were not carried out across the four groups. Survival in patients with biopsy-proven lupus nephritis was analyzed using Cox regression analysis. Time was calculated from the time of first diagnosis of biopsy-proven class III, IV, or V nephritis to death. Given that TA variables may be highly correlated with time to event, in addition to reporting the relationship between TA variables and survival, we calculated the mean proteinuria and average MAP during the first 2 years of follow-up after kidney biopsy, and related this variable to survival in all patients who had these data available for analysis ($n=50$). Therapeutic interventions are described in the Supplementary Table S1 online.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Table S1. Therapeutic interventions.

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