Nephrol Dial Transplant (2012) 27: 1472–1478
doi: 10.1093/ndt/gfr517
Advance Access publication 19 September 2011

Strategy for second kidney biopsy in patients with lupus nephritis

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Abstract

Background. Standard clinical and laboratory parameters have limited predictive values for discriminating between active lupus nephritis and chronic disease. The objective of this study was to examine the predictive utility of a second kidney biopsy in patients with lupus nephritis.

Methods. Patients with lupus nephritis were advised to have second kidney biopsies at the end of the maintenance phase of their therapies. Baseline and second renal biopsies were re-classified by pathologists blinded to the clinical data. The relationships between remission status and histological parameters were examined.

Results. Included in this study were 77 patients followed up for a median duration of 8.7 years (interquartile range, 5.3–10.1 years). Their renal survival rates were 93% for those in complete remission (CR), 69% for partial remission (PR) and 41% for no remission (NR). One-third of the patients with PR and 14% of patients with NR had no histological evidence of active disease on second biopsy. At the second biopsy, but not at the baseline biopsy, activity index was predictive of survival. The 10-year renal survival rate was 100% for those with an activity index of 0, 80% for those with an activity index of 1 or 2 on the second biopsy and 44% for those with an index of >2, regardless of remission status.

Conclusion. Second kidney biopsy at the end of maintenance phase of therapy is an important diagnostic and prognostic tool that could guide physicians to safer practices with better outcomes.

Keywords: kidney biopsy; lupus nephritis; systemic lupus erythematosus

Introduction

The goals for managing patients with lupus nephritis include early diagnosis and proper therapy, especially in the beginning stages of the disease, when prompt and optimal therapy may prevent irreversible damage, without exposure of patients to the side effects of immunosuppressive therapy [1]. To achieve such goals, and given the limited reliability of clinical and laboratory data, it is clear that renal biopsy is essential in assessing disease activity and guiding treatment [2, 3]. This is especially true in the majority of patients that will continue to have partial remission (PR) or no remission (NR) [4, 5] A second biopsy in lupus nephritis may detect unsuspected active disease. Conversely, the identification of quiescent disease may help to reduce the iatrogenic sequelae resulting from the toxicity of the drugs used for treatment. The main objective of our study was to examine the predictive utility of a strategy of second biopsy in lupus nephritis and to correlate findings of second biopsies with remission status.

Materials and methods

Consecutive patients with systemic lupus erythematosus (SLE) nephritis presenting to King Khaled University Hospital, Riyadh, Saudi Arabia, were invited to participate in a longitudinal study on the predictive power of second kidney biopsy and long-term outcome of renal function. Patients were enrolled between November 1996 and April 2009 for first kidney biopsy.

Patients were eligible for this study if they had SLE, as defined by the American Rheumatism Association [6], and had biopsy-proven lupus nephritis. Patients were advised to have a second biopsy to assess disease activity at the end of the maintenance phase, 12–18 months from the initiation of induction.

Patients were followed for a median of 8.7 years [interquartile range (IQR), 5.3–10.1 years] beginning in 1996. Their clinical and biochemical parameters were collected annually. In addition, specimens of baseline renal biopsies were re-accessed and were re-examined by light, immunofluorescence and electron microscopies, and they were categorized according to the ISN/RPS (International Society of Nephrology and Renal Pathology Society) classification protocol [7, 8] by two renal pathologists who were unaware of the patients' clinical data or timing of kidney biopsies. Activity and chronicity indices were determined according to the scoring system of Pollak *et al.*, as modified by Austin *et al.* [9, 10].

Outcome variables

We compared each patient's ISN/RPS class between the first and second biopsies. We also examined the probability of the doubling of initial serum creatinine at the final follow-up visit. Complete remission (CR) was defined as a serum creatinine level of ≤125 μmol/L and proteinuria of ≤0.33 g/day at the time of the second biopsy. PR was defined as a ≤25% increase in baseline creatinine and a ≥50% reduction in baseline proteinuria to ≤1.5 g/day (but >0.33 g/day) [11]. Renal relapse was defined as a doubling of the proteinuria or by an increase of serum creatinine by 50% [12]. All patients with ISN/RPS Class III or IV disease received induction therapy—consisting of corticosteroids and a maximum of six monthly boluses of intravenous cyclophosphamide (0.5–1.0 g/m^2 of body surface to induce a leucocyte count no. <2000 cells/mm^3). After induction, the patients were given either 0.5–1.0 g of intravenous cyclophosphamide per square meter of body surface every 3 months or 1–3 mg of oral azathioprine per kilogram of body weight per day. Since the introduction of mycophenolate mofetil (MMF) in 2004, this drug has been used in both the induction and maintenance phases of therapy, in addition to the above protocol. Patients with Class II lupus nephritis were treated with corticosteroids and azathioprine at a dose of 2–3 mg/kg/day. Patients who relapsed were treated according to the induction therapy protocol. For those who were on azathioprine maintenance therapy, the dose of prednisolone, as well as of azathioprine, was increased if the azathioprine dose had been tapered before the confirmation of relapse. For those patients who received MMF as a maintenance therapy, MMF was either restarted or its dose increased to 2-3 g/day. Cyclophosphamide use for the treatment of relapse was only administered to those who failed to respond to MMF or azathioprine. All therapy options were left to the discretion of the physician and patient. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analyses

The categorical variables are presented as absolute numbers and percentages and the continuous ones as mean ± SD. The normality assumption was checked using the Shapiro–Wilk test. To compare categorical data of clinical, laboratory and pathological relevance, we used the chi-square test and Fisher's exact test—and for continuous variables the Kruskal–Wallis test. For multiple comparisons, we used Dunn's test. Survival analysis was used to evaluate the relationship between remission status and histological lesions and renal outcome. For this purpose, the activity indices and chronicity indices derived from renal biopsies were categorized. The activity indices and chronicity indices were categorized into three groups 0, 1–2 and >2, and <3, 3–6 and >6, respectively. Associations between histological and clinical variables, and the risk of the doubling of serum creatinine were subjected to Cox regression analyses. The likelihood-ratio test was used to assess the statistical significance of any association between remission status, activity indices, chronicity indices and the risk of the main outcome and study endpoint, which were the doubling of serum creatinine. All models were adjusted for age, gender, ISN/RPS class, complement levels, anti-nuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA) antibodies level urine sediments and proteinuria. The survival time was defined as the interval from the time of the first biopsy until doubling of serum creatinine or last follow-up. Using the 5% significance level, $P \leq 0.05$ was considered significant.

Results

Of the 85 patients originally included, 8 refused a second biopsy and were thus excluded. A total of 77 patients completed the study and were included in the data analysis. The mean duration of affliction with SLE before first biopsy was 2.2 ± 2.8 years. The mean age (SD) of the participants was 27.9 (SD: 9.7) years. The cohort was followed for a

Table 1. Characteristics of patients at the beginning of induction therapy[a]

Age (year)	27.9 ± 9.7
Male, *n* (%)	11 (14.3%)
Renal biopsy according to Class, *n* (%)	
II	8 (10.4)
III	27 (35.1)
A	6 (22.2)
AC	10 (37.1)
C	11 (40.7)
IV	28 (36.4)
Global	
A	6 (28.6)
AC	13 (61.9)
C	2 (9.5)
Segmental	
A	3 (42.9)
AC	3 (42.9)
C	1 (14.3)
V	7 (9.1)
III or IV and V	6 (7.8)
VI	1 (1.3)
Serum creatinine (μmol/L)	
Median	77.5
IQR	61.5–120
Urine protein (g/24-h urine sample)	
Median	1.3
IQR	0.53–3.8
Nephrotic range proteinuria, *n* (%)	17 (22.1)
Serum complement 3 (mg/mL)	
Median	0.75
IQR	0.4–1.11
Serum complement 4 (mg/mL)	
Median	0.16
IQR	0.06–0.34
Anti-dsDNA antibodies (IU/mL)	
Median	273
IQR	0–987
Urine red cells (per HPF)	
Median	20
IQR	0–100
Activity index	
Median	3
IQR	1–9
Chronicity index	
Median	3
IQR	2–5

[a]Anti-dsDNA, anti-double stranded DNA antibodies (radioimmunoassay, normal: <7 U/mL); HPF, high-power field. Normal complement-3 is 0.9–1.8 g/L, normal complement-4, 0.1–0.4 g/L. Maximum score of activity index is 24, of chronicity index is 12.

median of 8.7 years (IQR, 5.3–10.1 years). Of the participants, 14.3% were male ($n = 11$) and 84.4% were native Saudi. Other baseline characteristics are shown in Table 1. Of the cohort, 18 patients (20.8%) received MMF, 8 patients received azathioprine (10.3%) and the rest received cyclophosphamide. Among those who were given cyclophosphamide, 55% (32 patients) received azathioprine for the maintenance phase of therapy.

CR occurred in 32 patients (41.6%) and PR in 18 patients (23.4%). There was no relationship between baseline proteinuria, urine sediments, complement levels, anti-dsDNA antibodies level, activity or chronicity indices and the probability of achieving CR, PR or NR (Table 2). The mean cumulative doses of cyclophosphamide given were not significantly different between the three groups (Table 3). At 6 months after the first biopsy, median serum creatinine was 76 μmol/L (mean 113 ± 158), median proteinuria 0.44 g/day (mean 1.2 ± 1.7), median anti-dsDNA antibodies 129 U/mL, median complement 3 (C3) 1.04 g/L (IQR: 0.84–1.45) and median complement 4 (C4) was 0.26 g/L (IQR: 0.16–0.32). Logistic regression analysis did not show any association between the rate of doubling of serum creatinine and 6-month proteinuria, serum creatinine, ANA complement levels or anti-dsDNA titre.

At the time of the second biopsy, the only statistically significant association observed was between C3 level and remission status: patients with NR had significantly lower C3 levels. However, other laboratory markers for lupus nephritis at the time of the second biopsy, including haematuria pyuria, anti-dsDNA and C4 levels, were not different between those with CR, PR or NR (Table 3).

Table 4 shows the comparison of the ISN/RPS classifications of the first and second biopsies for the 144 biopsies, which were reassessed or assessed (77 first biopsies, 77 second biopsies). On second biopsy, 32 participants (41.6%) had no shift in their ISN/RPS class. Of 55 patients who had pure Class II–IV at their first biopsy, 20% had histological shifts to another class in the second biopsy—however, none of them changed to pure Class V. The incidence of change from one class to another classes was 60% in 15 participants with NR, 41.2% in 7 participants with PR and 65.7% in 23 participants with CR. Of note, the proportion of patients with ISN/RPS Classes III and IV were not significantly different between the three groups of CR, PR and NR.

Doubling of serum creatinine was eventually noted in 21 patients; 76% (10 patients) of these patients had ISN/RPS Class III or IV in their initial biopsies. The rate of the doubling of serum creatinine was significantly higher in those with PR and NR compared with those who achieved CR ($P < 0.001$) (Figure 1). The renal survival rate at 10 years was 93% for CR, 69% for PR and 41% for NR. The relative risk for doubling of serum creatinine was 1.34 [confidence interval (CI): 0.97–1.84] for patients with PR and 2.14 (CI: 1.37–3.36) for those with NR.

Of patients with CR and PR, 34 (68%) had renal exacerbations. There was no significant difference in the occurrence of relapse between complete and partial responders ($P = 0.5$). Overall, 72% of those who had PR relapsed compared with 65% of those who achieved CR. The rate of the doubling of serum creatinine was similar among those who never relapsed and those who had relapsed (12.5 and 11.8%, respectively).

The second kidney biopsy showed the persistence of endocapillary proliferation or hypercellurity in 50% of patients, leucocyte infiltration in 28% and interstitial deposits in 71% (Table 5). The majority of the instances of cellular crescents and fibrinoid necrosis or karyorrhexis had resolved by the second biopsy (93 and 74%, respectively). The rate of the doubling of serum creatinine was statistically significant among those who had persistent endocapillary proliferation or hypercellularity and interstitial inflammation in comparison with those who had resolution of such lesions in the second biopsy (Table 5). There was a trend to a higher rate of doubling of serum creatinine among those who had fibrinoid necrosis, karyorrhexis or leucocyte infiltration but did not reach statistical significance (Table 5).

There were no differences in baseline activities or chronicity indices between those with CR, PR and NR (Table 2).

Table 2. Laboratory and histological characteristics of patients at the time of first biopsy[a]

	CR	PR	NR	P
Number of patients	32	18	27	
Activity index	2 (1–9)	3 (1–9)	4 (0–8)	0.9
Chronicity index	2.5 (2–4.5)	4 (2–6)	3 (2–5)	0.6
Anti-dsDNA (IU/mL)	257 (0–749)	256 (116–699)	368 (0–1397)	0.6
Urinalysis red cells (per HPF)	30 (0–200)	25 (0–50)	10 (0–50)	0.6
Serum complement 3 (mg/mL)	0.73 (0.34–1.07)	0.9 (0.58–1.06)	0.54 (0.37–1.12)	0.8
Serum complement 4 (mg/mL)	0.20 (0.06–0.34)	0.18 (0.11–0.3)	0.1 (0.06–0.3)	0.6
24-h urine protein (g/day)	0.76 (0.41–2.23)	1.7 (0.85–5.03)	1.94 (0.72–4.55)	0.3
Serum creatinine (μmol/L)	77 (60–120)	78 (61–121)	75 (62–119)	0.1
ISN/RPS, *n* (%)				
Class III	15 (55.6)	4 (14.8)	8 (29.6)	0.03
Class IV	11 (39.3)	8 (28.6)	9 (11.7)	0.8

[a]Data are expressed as median (IQR). Anti-dsDNA, anti-double stranded DNA antibodies. HPF, high-power field. P-values were calculated with the use of Kruskal–Wallis test for continuous variables, and with the use of the chi-square test and Fisher's exact test for categorical variables.

Table 3. Laboratory and histological characteristics of patients at the time of second biopsy[a]

	CR ($n = 32$)	PR ($n = 18$)	NR ($n = 27$)	P
Activity index	1 (0–2)	2 (0–3)	3 (1–9)	0.001
Chronicity index	4 (2–7)	5 (2–6)	6 (5–7)	0.2
Anti-dsDNA (IU/mL)	0 (0–613)	402 (0–1223)	188 (0–615)	0.3
Urinalysis red cells (per HPF)	0 (0–10)	5 (0–90)	30 (0–120)	0.3
Serum complement 3 (mg/mL)	1.3 (1.2–1.59)	0.97 (0.83–1.58)	0.77 (0.54–0.95)	<0.001
Serum complement 4 (mg/mL)	0.27 (0.19–0.37)	0.28 (0.09–0.34)	0.22 (0.12–0.34)	0.5
Cumulative cyclophosphamide dose-gram	6.6 ± 3.2 (7.2)	6.9 ± 3.1 (6.8)	7.9 ± 5.7 (6.6)	0.7
Proportion of those with activity index of 0	14 (40%)	5 (29.4%)	4 (16%)	0.1

[a]Data are expressed as median (IQR). Anti-dsDNA, anti-double stranded DNA antibodies; HPF, high-power field. P-values were calculated with the use of Kruskal–Wallis test for continuous variables, and with the use of the chi-square test and Fisher's exact test for categorical variables.

Table 4. Histological changes in ISN/RPS classifications at baseline and repeat biopsy[a]

	Repeated kidney biopsy ISN/RPS class							
Baseline ISN/RPS class	II	III	IV S	IV G	V	VI	V & III, V & IV	Total
II	4	2	0	2	0	0	0	8
III	7	10	0	7	0	0	3	27
IV S	0	1	0	1	0	0	2	4
IV G	1	10	3	7	0	2	1	24
V	0	0	0	0	4	0	3	7
VI	0	1	0	0	0	0	0	1
V & III, V & IV	0	1	0	1	0	1	3	6
Total	12	25	3	18	4	3	12	77

[a]S, segmental; G, global.

The median renal activity index of the first biopsy was 2 (IQR: 1–9) for those with CR, 3 (IQR: 1–9) for those with PR and 4 (IQR: 0–8) for those with NR (P= 0.9) (Table 2). Similarly, the median chronicity index in the first biopsy was 2.5 (IQR: 2–4.5) for those with CR, 4 (IQR: 2–6) for those with PR and 3 (IQR: 2–5) for those with NR (P = 0.7) (Table 2). However, the activity, but not the chronicity, indices were significantly different between the three groups at the second biopsy (Table 3). The median activity index was 1(IQR: 0–2) for the CR group, 2 (IQR: 0–3) for those with PR and 3 (IQR: 1–9) for those with NR (P = 0.001). In a logistic regression, the activity index at the second biopsy, but not the one at baseline, predicted the renal outcome (P < 0.001 versus P < 0.688, respectively) (Figures 2 and 3). All of the patients whose serum creatinine doubled possessed activity indices >0 at the time of their second biopsy, regardless of their remission status. The relative risk for the doubling of serum creatinine was 1.4 (CI: 1.1–1.8) for those with an activity index of 1 or 2 and 1.68 (CI: 1.3–2.2) for patients with an activity index >2 at the time of second biopsy. The renal survival rate at 10 years was 100% for those with activity indices of 0, 80% for those with activity indices of 1 or 2 and 44% for those with activity indices >2 (Figure 3).

The chronicity index of the baseline biopsy did not significantly predict poor renal outcomes (relative ratio: 0.94; CI: 0.75–1.19) (Figure 4). In none of those with chronicity indices of <3 at the second biopsy did serum creatinine double, while it did in 40.8% of those with chronicity indices of 3–6 (relative ratio: 1.69, CI: 1.34–2.13) and 54.2% of those with chronicity indices of ≥7 (relative ratio: 2.18, CI: 1.41–3.37). The renal survival rate at 10 years was 100% for those with chronicity indices of <3, 73% for those with chronicity indices of 3–6 and 55% for those with chronicity indices ≥7. The predictive power for renal survival of the chronicity index at the time of the second biopsy did not reach statistical significance, but there was a trend toward a better outcome in those with chronicity indices <3 (Figure 5).

Discussion

With respect to the management of patients with lupus nephritis, our study has shown the clinical relevance of a second kidney biopsy in assessing disease activity at the end of the maintenance phase of therapy before withdrawing immunosuppressive treatment. Additionally, the histological parameters of active disease more reliably predict renal outcomes, defined in our study as the doubling of serum creatinine, than does remission status. Only 40% of patients with CR had no histological evidence of active disease, and only 7% had doubling of serum creatinine. Therefore, remission status lacks sensitivity and specificity for differentiating renal activity and damage in lupus nephritis. In clinical practice, remission in lupus nephritis is defined based on serum creatinine and proteinuria. However, significant kidney damage can occur before renal function is impaired and before the damage can be detected by laboratory tests. Similarly, persistent proteinuria may not necessarily indicate ongoing renal inflammation—it may be due to pre-existing chronic lesions. Our study reconfirmed the findings of others, that clinico-biochemical parameters alone are not sufficient to assess disease activity [2, 3]. Obtaining a kidney biopsy at baseline only is therefore not sufficient, because findings in the first biopsy cannot accurately be predictive of the renal outcome. Most studies that examined various treatment options were able to induce CR in only 30–40% of patients, at best [13, 14]. Typically, clinicians either increase or modify immunosuppressive treatments for patients with PR or NR. However, our study has shown that one-third of patients with PR and 14% of those with NR have no histological evidence of active disease at the end of the maintenance phase. Therefore, it is futile and harmful to boost immunosuppressive regimens in such patients without repeating the kidney biopsy.

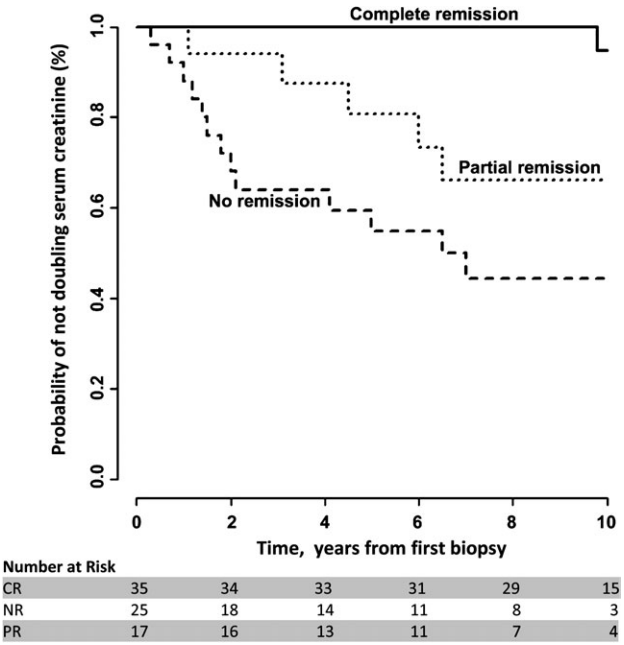


Fig. 1. Renal survival in patients with lupus nephritis based on remission status. The renal survival was significantly in patients with CR and PR ($P < 0.0001$; log-rank test).

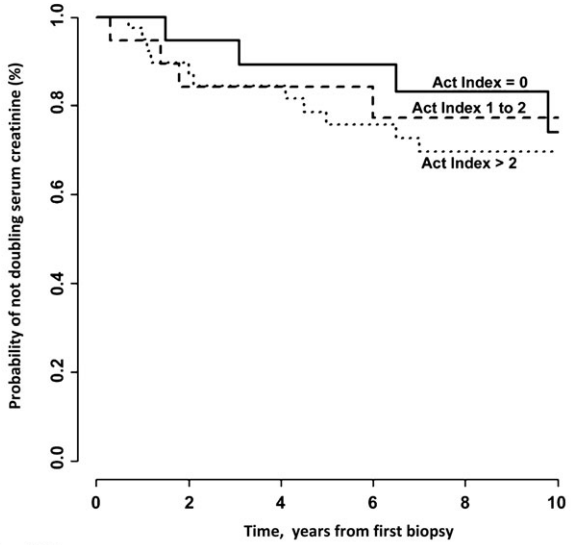
Almost two-thirds of the participants in our study had a change of classification of disease based on the second biopsies. Daleboudt *et al.* [15] retrospectively examined histological changes in 35 patients with lupus nephritis who had two or more kidney biopsies . They, like us, observed that patients with proliferative lesions in the original biopsy, in contrast to those with non-proliferative lesions, rarely switch to a pure non-proliferative nephritis during a flare-up. Although relapses have been linked to reduced renal reserve, it is of interest to note that the rate of the doubling of serum creatinine is similar between relapsers and non-relapsers. This has also been reported by other studies, and is possibly related to early detection and prompt re-induction of remission [16].

Several studies have found the activity index to be a significant predictor of renal outcome [17–19]. In contrast, others have reported no significant correlation between activity index and outcome [20–22]. Our study has shown the importance of the activity index in the second biopsy (but not in the baseline biopsy) in predicting a poor renal outcome, as based on the doubling of serum creatinine. This is in agreement with what Hill *et al.* [23] have reported. In general, the clinical significance of a low-activity index, and the need to modify treatment, is not clear. We found that even a low-activity index of 1 or 2 at the second biopsy

Table 5. Comparison of risk of doubling serum creatinine in relation to response of active histological parameters to treatment[a]

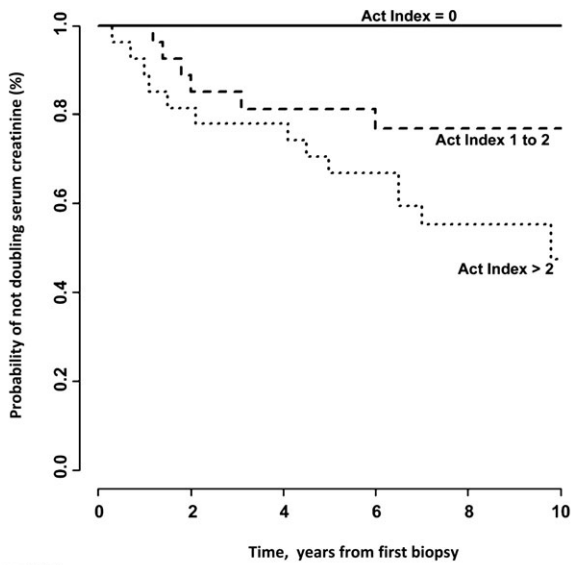
	Baseline biopsy	Repeated biopsy			
			Doubling serum creatinine		
Types of active lesion	No. of patients with active lesion	No. of patients with persistent active lesion	Active lesion *N* (%)	Recovered *N* (%)	P-value
Endocapillary prolif. or hypercellu.	42	21	10 (47.6%)	2 (9.5%)	0.04
Leucocyte infiltration	39	11	5 (45.5%)	6 (21.4%)	0.14
Subendothelial hyaline deposits	17	6	4 (66.7%)	3 (27.3%)	0.3
Fibrinoid necrosis/karyorrhexis	27	7	4 (57.1%)	4 (20%)	0.14
Cellular crescents	16	1	1 (100%)	5 (33.3%)	0.37
Interstitial inflammation	45	32	10 (31.3%)	0 (0%)	0.04

[a]Endocapillary prolif., endocapillary proliferation; hypercellu., hypercellularity. P-values were calculated with the use of the chi-square test and Fisher's exact test.



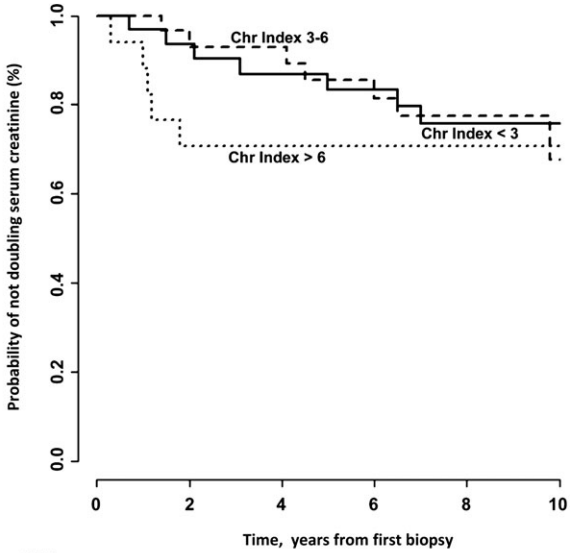
Number at Risk						
Act Index = 0	19	18	16	16	13	6
Act Index 1-2	19	16	15	12	9	5
Act Index > 2	39	34	29	25	22	11

Fig. 2. Renal survival in patients with lupus nephritis based on activity index at baseline biopsy. Survival analysis based on activity index (AI) value of 0, 1–2 and >2 at baseline biopsy demonstrated no prognostic significance of AI (P = 0.688; log-rank test).



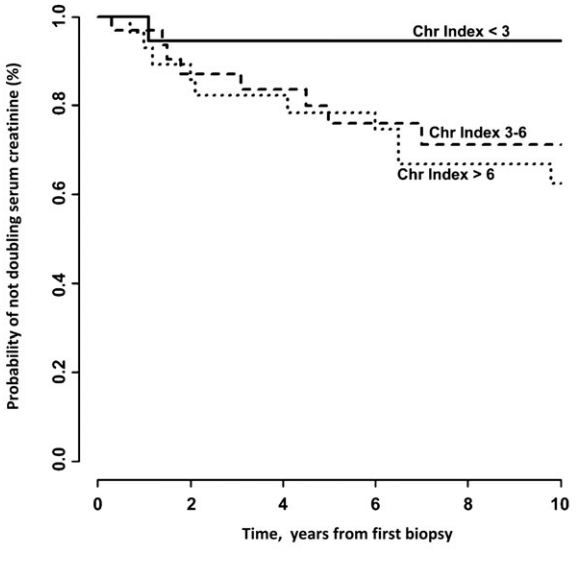
Number at Risk						
Act Index = 0	23	23	18	16	14	7
Act Index 1-2	27	23	21	19	17	11
Act Index > 2	27	22	21	18	13	4

Fig. 3. Renal survival in patients with lupus nephritis based on activity index at repeated biopsy. Survival analysis based on Activity Index (AI) value of 0, 1–2 and >2 demonstrated prognostic significance of AI (P < 0.001; log-rank test).



Number at Risk						
Chr Index < 3	31	29	26	24	19	11
Chr Index 3-6	29	27	25	21	17	7
Chr Index > 6	17	12	9	8	8	4

Fig. 4. Renal survival in patients with lupus nephritis based on chronicity index at baseline biopsy. Risk of doubling serum creatinine according to chronicity index (CI) value of <3, 3–6 and >6 showed no prognostic significance of CI (P = 0.75; log-rank test).



Number at Risk						
Chr Index < 3	18	17	16	15	13	5
Chr Index 3-6	31	26	22	17	15	4
Chr Index > 6	28	25	22	21	16	13

Fig. 5. Renal survival in patients with lupus nephritis based on chronicity index at repeated biopsy. Risk of doubling serum creatinine according to chronicity index (CI) value of <3, 3–6 and >6 showed no prognostic significance of CI (P = 0.095; log-rank test).

can be associated with a 40% increase in the risk of poor renal outcome. Chronicity indices at the baseline were not different in those with CR, PR or NR.

Our study highlights the importance of achieving CR or PR in patients with lupus nephritis. This finding is consistent with recent studies that have observed a better renal survival rate among even those with PR [11]. This, however, should not deter clinicians from pursuing the primary goal of achieving CR because renal survival rates in these patients remain far greater than in those with PR. Still, patients with PR or NR, and who also had no evidence of active disease at the second biopsy, had higher renal

survival rates. It would therefore seem logical to suppose that, patients with PR or NR, perhaps even more than patients with CR, require a second biopsy to assess disease activity before modification of their immunosuppressive regimens.

The optimal use of immunosuppressive agents depends on the knowledge of the activity status of the nephritis. The tests that are needed for this assessment ideally should be simple, non-invasive and capable of discriminating between active inflammation and chronic disease. Urine may be the ideal medium to which to apply candidate tests because it might contain the products of allo-activated or cytotoxic cells [24], chemokines, cytokines [25, 26] and the patterns of proteins detected by proteomic techniques [27]. Detection of active disease by such non-invasive means may allow tailoring of the intensity of immunosuppression to the disease activity, which may result in the reduction of both the unwanted side effects of immunosuppression and the incidence of renal failure. However, pending the availability of such tests, a second kidney biopsy will, as our study has shown, continue to be the most sensitive test to assess disease activity. The ideal timing for the second biopsy is not known. Hill *et al.* performed a second biopsy at the end of the induction phase. However, most patients need to continue receiving immunosuppressive treatment during the maintenance phase. We therefore believe that the optimal time for a second biopsy is at the end of the maintenance phase, when patients have finished the treatment course.

Because achieving remission alone is not a sufficient target for the prediction of poor renal outcomes, good or poor, we conclude that, in the management of lupus nephritis, a strategy of a second biopsy at the end of the maintenance phase should guide ongoing therapy with the least side effects.

Conflict of interest statement. None declared.

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Received for publication: 22.1.11; Accepted in revised form: 1.8.11