Kidney International, Vol. 50 (1996), pp. 2047–2053

"Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis

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"Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. We retrospectively analyzed the courses of 70 patients with lupus nephritis followed for 5 to 30 years (median 127 months). Patient survival was 100% at 10 years and 86% at 20 years. The probability of not reaching the end point (persistent doubling of plasma creatinine) was 85% at 10 years and 72% at 20 years. A multivariate analysis of variables at presentation showed that male sex ($P = 0.005$) and hematocrit lower than 36% ($P = 0.01$) were associated with the end point (relative risk 7.5 and 14). We then analyzed for the role of renal flare-ups, defined either as a rapid increase in plasma creatinine or by an increase in proteinuria. Patients with renal flares of any type had more probabilities of reaching the end point than patients who never had flares ($P = 0.03$; relative risk 6.8). The hazard of the end point was 27 times higher in patients with flares along with rapid increased in plasma creatinine than in patients without flares or with flares with proteinuria alone ($P < 0.00001$). This hazard was higher when plasma creatinine did not return to the basal levels within two months after treatment ($P < 0.0001$).

Renal disease is a frequent complication of systemic lupus erythematosus (SLE) that can heavily influence the prognosis. The mortality rate is higher for SLE patients with nephritis than for those without renal involvement [1, 2], and some 10 to 60% of SLE patients with nephritis eventually develop end-stage renal disease [3–8]. A number of studies have looked for which clinical and histological features at presentation might be predictive of outcome in the long-term. However, the conclusions of these studies have not all agreed [5–20]. This was not completely unexpected, in view of the different criteria for selection, the heterogeneity of the disease and the different therapeutic schedules used.

In this study we reviewed the outcome of 70 patients with lupus nephritis, all of whom had had follow-ups of at least five years. The initial outcome of 21 of these patients was reported before [21]. All patients were submitted to renal biopsy, were followed by a single institution and were given treatment with homogeneous criteria. For this particular series, we investigated not only the prognostic value of clinical and histological features at presentation but also the possible prognostic role of exacerbations of lupus nephritis, which has never been taken into account in previous analyses.

Received for publication February 8, 1996
and in revised form June 25, 1996
Accepted for publication June 27, 1996

Methods

Patients

Criteria for inclusion in this study were: (i) a histological diagnosis of lupus nephritis with a daily urine protein excretion of more than 1 g per day, and/or an elevated plasma creatinine; (ii) four or more signs and symptoms of SLE [22]; (iii) a follow-up of at least five years. Patients with a creatinine clearance lower than 20 ml/min for more than three months prior to admission were excluded. According to these criteria three patients with rapidly progressive glomerulonephritis and creatinine clearance between 8 and 15 ml/min were included, while eight patients with chronic renal failure were not admitted. All these eight patients reached the end-stage renal disease in a median period of one month. Glomerular lesions were classified according to the WHO classification [23]. The activity and chronicity indices were assessed according to Austin et al [16].

Patients were evaluated clinically and biochemically at least once a month if any sign or symptom of renal activity was present. Patients with normal plasma creatinine, proteinuria less than 0.2 g per day, and inactive urine sediment were evaluated every three to six months and whenever patients complained of any symptom.

Definitions

The end point of the study was defined as the doubling of plasma creatinine lasting for at least six months with a value of plasma creatinine of at least 2 mg/dl. Renal insufficiency was defined as plasma creatinine equal to or higher than 1.5 mg/dl. Complete remission was defined as proteinuria less than 0.2 g per day, with normal renal function. Nephrotic proteinuria was defined by a daily urine protein excretion of more than 3.5 g per day; non-nephrotic proteinuria was defined as urinary protein excretion between 0.2 and 3.5 g per day. Arterial hypertension was defined as a supine diastolic blood pressure higher than 90 mm Hg in three consecutive measurements. Serum C3 levels lower than 55 mg/dl and serum C4 levels lower than 20 mg/dl were considered to be low.

A renal flare-up was arbitrarily defined as: (i) "nephritic flare" characterized by an increase in plasma creatinine of at least 30% over the last value associated with nephritic urinary sediment and

generally increased proteinuria. This definition did not include patients with chronic slower increase in plasma creatinine who were considered not to have "nephritic flare" but as having a progressive chronic renal failure. (ii) "Proteinuric flare" was characterized by an increase in proteinuria without modification of plasma creatinine. Proteinuria had to increase by at least 2 g per day if the basal proteinuria was less than 3.5 g per day, or be doubled if patient already had a nephrotic proteinuria [21].

Therapy

Three patients with normal renal function and non-nephrotic proteinuria were never treated during the follow-up. In two of them who were diagnosed with membranous nephritis, one followed for 11 and one for 14 years, proteinuria slowly decreased until complete remission. In the third patient, with focal proliferative nephritis, proteinuria persisted around 1 g per day until the last observation, five years after presentation. One patient with membranous nephropathy and non-nephrotic proteinuria was not treated for six years. Then nephrotic syndrome developed and the patient was submitted to three intravenous methylprednisolone pulses followed by oral prednisone, 0.5 mg/kg per day.

Nineteen patients admitted to our Unit before 1976 (10 with diffuse proliferative nephritis, 7 with membranous nephritis and 2 with focal proliferative nephritis) were given oral prednisone, 1 mg/kg per day for one month, gradually reduced to a maintenance dose of 10 to 15 mg per day. In this group, 13 patients with more severe renal and extrarenal disease were also treated with immunosuppressive agents: 8 patients were given azathioprine for a median period of 11.5 months (25th and 75th percentile, 8.7 and 12), 1 patient was given chlorambucil for six months, 4 patients were given oral cyclophosphamide for a median period of eight months (25th and 75th percentile, 3.7 and 12). Another 47 patients were admitted to our Unit after 1976 (32 with diffuse proliferative nephritis, 11 with membranous nephritis and 4 with focal proliferative nephritis). All of them were initially treated with three consecutive intravenous methylprednisolone pulses (0.5 to 1 g every 24 hr according to the body wt) followed by oral prednisone (0.5 to 1 mg/kg per day), gradually tapered to 10 to 15 mg per day as maintenance therapy. For 29 patients with more severe renal and extrarenal disease, immunosuppressive agents were added: azathioprine for 12 patients for a median period of seven months (25th and 75th percentile, 5.7 and 10), chlorambucil for 11 patients for a median period of three months (25th and 75th percentile, 1.5 and 4), oral cyclophosphamide for 6 patients for a median period of two months (25th and 75th percentile, 1 and 3).

Before 1976, the flare-ups were treated with prednisone, 1 mg/kg per day for 15 to 30 days, then gradually tapered; after 1976 the flare-ups were treated with three intravenous methylprednisolone pulses (0.5 to 1 g each), followed by a reinforcement of oral prednisone (0.5 to 1 mg/kg per day) and by the introduction of immunosuppressive agents for the more severe cases.

Statistical analysis

The study end point was the persistent doubling of plasma creatinine. For the two patients who died, the last plasma creatinine before death was considered. The following clinical and histological parameters at study entry were analyzed for predictive value: duration of lupus nephritis before admission, sex, age, serum creatinine, daily urine protein excretion, arterial hypertension, serum albumin levels, hematocrit, platelets, blood white cells, serum C3 levels, serum C4 levels, number of extra-renal symptoms, WHO histological classification, activity index, chronicity index. In addition, the predictive value of nephritic flares was analyzed. The above-mentioned clinical and histological factors were evaluated for the prediction of renal flares together with therapeutic strategies (treatment with or without methylprednisolone pulses, amount of prednisone at 3, 6, 12 months, treatment with of without cytotoxic agents). Data management and analysis were performed with the S-Plus Statistical Package [24]. Median and interquartile range values were used as descriptive statistics, because of the non-normal distribution of most variables. The non-parametric Wilcoxon test was used to compare two sample medians of continuous variables. The cumulative survival curves were derived by the Kaplan-Meier method [25], and the differences between two survival curves were checked by the log-rank or Mantel-Haenszel test [26]. The influences of prognostic factors on the risk for both chronic renal failure and nephritic flares with rapid increase in plasma creatinine were investigated by the Cox proportional hazard regression model [27]. Both uni- and multivariate analyses were performed. The Harrell z-test on Schoenfeld residuals was used to examine the proportional hazard assumption for each covariate [28]. Logarithmic transformation was used on variables showing skewed distribution, before entering them in the regression models. Model selection was performed by heuristic searches through a number of candidate models. Stepwise regression algorithms were not used, because the sample size was not large enough to guarantee the reliability of automatically selected models. A threshold value was found for some of the continuous variables that were significant at the univariate Cox regression model: the threshold was defined as the value that maximized, with the least group size imbalance, the difference between the survival curves of the groups of patients individualized by the value itself. It is clear that different thresholds could be found for the same variable when predicting different outcomes.

Relative risks and their 95% confidence interval (CI) have been derived, after fitting the Cox propotional hazards model, as the antilogarithm of the coefficient estimated for each covariate included in the model. As an alternative procedure, the relative risk due to a binary variable has been calculated using the log-rank approach, that is, computing the ratio between the differences (observed failures − expected failures) in the two patient groups indivituated by the variable itself. Very similar results were obtained by the two methods, and in the following only those derived from Cox model will shown.

Results

Clinical characteristics at presentation

Seventy patients (65 female and 5 male), median age 28.5 (25th and 75th percentile, 21 and 33) entered this study. The median duration of lupus nephritis before admission was three months (25th and 75th percentile, 0.2 and 7.1). Twenty-one patients (30%) had renal insufficiency at presentation (median plasma creatinine 1.8 mg/dl, 25th and 75th percentile, 1.6 and 2.4). All had proteinuria (median 3.3 g per day; 25th and 75th percentile, 1.8 and 4.9), which was in a nephrotic range in 33 patients (47%). Twenty-four patients (34%) had arterial hypertension. Serum C3 was low in 42 patients and serum C4 in 46 (Table 1). Renal biopsies showed diffuse proliferative nephritis (Class IV) in 42

Table 1. Clinical, biochemical, and histological features at presentation

Variable at presentation	All patients (70)	Patients with end point (14)	Patients without end point (56)	P^a
Duration of renal disease before study entry, *months* (m)	3	2.5	3.0	0.46
Sex				0.003
men (*N*)	5	4	1	
women (*N*)	65	10	55	
Age, *years* (m)	28.5	29	27.5	0.84
Serum creatinine, *mg/dl* (m)	1	1.55	0.9	0.09
Proteinuria, *g/day* (m)	3.3	3.5	3.1	0.7
Arterial hypertension (*N*)	24	7	17	0.15
Albumin, *g/dl* (m)	2.7	2.95	2.7	0.23
Hematocrit				0.0015
< 36% (*N*)	37	13	24	
≥ 36% (*N*)	33	1	32	
Platelet count, */mm³* (m)	224000	200000	240000	0.97
White blood cells count, */mm³* (m)	5550	5800	5350	0.4
Low C3 (*N*)	42	8	34	0.5
Low C4 (*N*)	46	9	37	0.9
Extrarenal symptoms (m)	3.0	3.5	3.0	0.07
W.H.O.				0.2
III (*N*)	7	0	7	
IV (*N*)	42	9	33	
V (*N*)	21	5	16	
Activity index (m)	7	6	7.5	0.3
Chronicity index				0.02
≥ 5 (*N*)	8	3	5	
< 5 (*N*)	62	11	51	

Values are expressed either as number of patients (*N*) or as median (m).

[a] *P* values refer to the statistical significance of the variables either in the Cox proportional hazard regression (for a continuous variable) or in the log-rank test for survival curves difference (for a discrete or discretized variable).

patients, focal proliferative nephritis (Class III) in 7 patients, and membranous nephritis (Class V) in 21 patients. The median activity index was 7 (25th and 75th percentile, 2 and 10) and the median chronicity index was 2 (25th and 75th percentile, 0.5 and 10). At presentation arthralgias were present in 66 patients (94%), fever in 54 patients (77%), cutaneous involvement in 53 patients (76%), pericarditis in 14 patients (20%), pleuritis in 13 patients (19%), and cerebritis in 8 patients (12%).

Outcome

Patients were followed for 5 to 30 years (median 127 months; 25th and 75th percentile, 90 and 181). The patient survival rate was 100% at 5 and 10 years and 86% at 20 years. Two patients died, one of cerebral hemorrhage after 15 years and one of lung cancer after 12 years of observation, when their plasma creatinines were 2.8 and 0.9 mg/dl. The probability of not reaching the end point was 94% at five years, 85% at 10 years and 72% at 20 years (Fig. 1). Fourteen patients (20%) reached the end point after a median period of observation of 119 months (25th and 75th percentile, 77 and 139.6). Four of them had to be submitted to dialysis; the other 10 patients had a median plasma creatinine of 2.3 mg/dl (25th and 75th percentile, 2 and 3) at the last observation. The remaining 56 patients had a median plasma creatinine of 0.8 mg/dl (25th and 75th percentile, 0.7 and 0.9) after a median follow-up of 125 months (25th and 75th percentile, 86.1 and 175.6). At the last observation, 27 of these patients had been in complete remission for a median period of 86.2 months (25th and 75th percentile, 40.6 and 117.6), 27 had non-nephrotic proteinuria (median 1.2 g per day; 25th and 75th percentile, 0.6 and 1.8) and 2 had nephrotic proteinuria (3.5 and 4.2 g per day; Table 2).

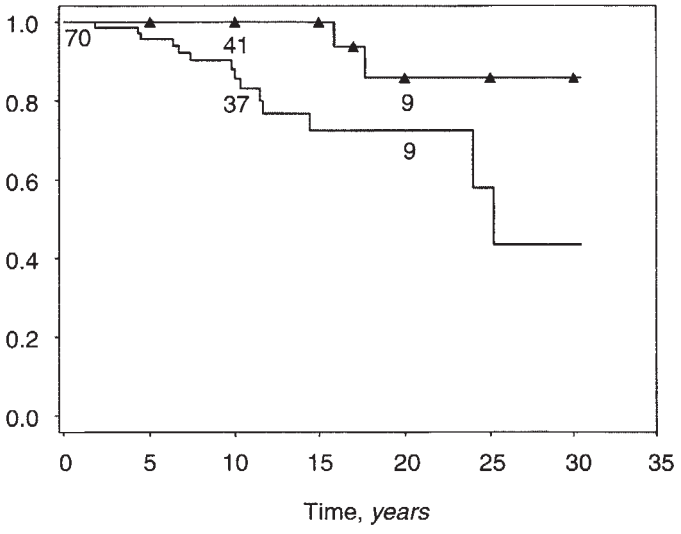

Fig. 1. *Probability of patients survival (▲) and probability of patients survival without end point (persistent doubling of plasma creatinine) (solid line).* Numbers on the curves indicate the number of patients who remain at risk.

A univariate analysis was performed to see whether any clinical or histological data at presentation might predict the long-term renal outcome. Male sex ($P = 0.003$), chronicity index higher than 5 ($P = 0.02$) and hematocrit lower than 36% ($P = 0.0015$) at presentation were significantly associated with the probability of reaching the end point (Table 1). By multivariate analysis, only

Table 2. Clinical status at the last follow-up

	All patients (70)	Patients without renal flares (24)	Patients with any type of renal flares (46)	Patients with "proteinuric flares" (25)	Patients with "nephritic flares" (21)
Doubling of plasma creatinine[a]	14 (20%)	1 (4.2%)	13 (28.3%)	0	13 (62%)
Normal renal function with nephrotic syndrome	2 (3%)	0	2 (4.3%)	2 (8%)	0
Normal renal function and non-nephrotic proteinuria[a]	27 (38.5%)	2 (8.3%)	25 (54.4%)	19 (76%)	6 (28%)
Complete remission	27 (38.5%)	21 (87.5%)	6 (13%)	4 (16%)	2 (10%)

[a] One patient per group died, the clinical status at the last follow-up before death is reported

male sex ($P = 0.005$) and low hematocrit ($P = 0.01$) were significantly associated with the end point. We checked for other threshold values but could not find any other significant cutpoint leading to less imbalance among groups both in univariate and multivariate analysis. A chronicity index of 6 was significant at multivariate analysis ($P = 0.01$), but the use of this cutpoint would have futher increased the imbalance between groups (5 vs. 63). The relative risk of reaching the end point was 7.5 for men (95% CI = 1.85 to 30.7) and 14 for patients with hematocrits lower than 36% (95% CI = 1.85 to 110.9).

Renal flares

Twenty-four patients (2 with focal proliferative nephritis, 12 with diffuse proliferative nephritis, 10 with membranous nephritis) never had renal flares during the median follow-up of 127 months (25th and 75th percentile, 84 and 186). The other 46 patients (5 with focal proliferative nephritis, 30 with diffuse proliferative nephritis, 11 with membranous nephritis) developed 114 renal flares during a median follow-up of 128 months (25th and 75th percentile, 99 and 177), which means 0.22 flare/patient/year. Twenty-one patients (1 with focal proliferative nephritis, 15 with diffuse proliferative nephritis, 5 with membranous nephritis) had 37 nephritic flares with a rapid change in renal function plus 25 flares with a change in proteinuria. The other 25 patients (4 with focal proliferative nephritis, 15 with diffuse proliferative nephritis, 6 with membranous nephritis) had 52 flares with a change in proteinuria.

In the group of patients who had no flares, only one patient (4%) reached the end point (plasma creatinine 2.3 mg/dl) after a follow-up of 87 months. The other 23 patients had a median plasma creatinine of 0.8 mg/dl (25th and 75th percentile, 0.7 and 0.9) after a median observation of 128 months (25th and 75th percentile, 80.1 and 188.2). At the last observation, two patients had non-nephrotic proteinuria (below 1 g per day in both) and 21 (87.5%) had been in complete remission for a median period of 86 months (25th and 75th percentile, 44.6 and 116.6; Table 2).

Twenty-one patients had 37 flares with rapid increases in plasma creatinine. In 3 of the 5 patients with membranous nephritis who developed such a type of flare, a control renal biopsy was done that showed transformation to diffuse proliferative nephritis in 1 patient and to diffuse proliferative nephritis plus membranous nephritis in 2 patients. The response was assessed two months after therapy. In 17 flares, the plasma creatinine returned to basal values after therapy; in 20 flares, the plasma creatinine remained above the basal values in spite of treatment. After a median period of observation of 120 months (25th and 75th percentile, 76 and 140), 13 (62%) of the 21 patients with nephritic flares had reached the end point. This happened less frequently in patients with complete responses to therapy ($P < 0.0001$). In 4 of these 13 patients, several flares characterized by proteinuria alone preceded the nephritic flares with increased plasma creatinine. Four patients had to be submitted to renal replacement therapy; the other nine patients had a median plasma creatinine of 2.5 mg/dl (25th and 75th percentile, 2.1 and 3.1) at the last observation. The remaining 8 patients who had nephritic flares had a median plasma creatinine of 0.9 mg/dl (25th and 75th percentile, 0.8 and 1) after a median follow-up of 123 months (25th and 75th percentile, 60 and 275). Six of these patients had non-nephrotic proteinuria (median 1.2 g/day; 25th and 75th percentile, 0.5 and 2) and 2 (10%) had been in complete remission, one for 117 and one for 157 months. No patient with flares characterized by proteinuria alone reached the end point. At the last observation (median 118 months; 25th and 75th percentile, 86 and 140), the median plasma creatinine was 0.8 mg/dl (25th and 75th percentile, 0.7 and 0.9), 2 patients had nephrotic proteinuria, 19 patients had non-nephrotic proteinuria (median 1.4 g per day; 25th and 75th percentile, 0.6 and 1.7) and 4 patients had been in complete remission for 7, 11, 37, 91 months, respectively (Table 2).

Since the median follow-ups of patients who had (128 months; 25th and 75th percentile, 99 and 177) or did not have renal flares (127 months; 25th and 75th percentile, 84 and 186; P = NS) were similar, the survival curves of these two groups were compared (Fig. 2). Patients who developed renal flares had significantly greater probabilities of reaching the end point than patients who never flared ($P = 0.03$, relative risk 6.8, 95% CI = 0.91 to 53.5). The median follow-up for patients who developed nephritic flares (135 months; 25th and 75th percentile, 108 and 200) was similar to that for the other patients (125 months; 25th and 75th percentile, 87 and 167; P = NS), allowing comparison of the survival curves of these two groups (Fig. 3). The probability of reaching the end point was significantly greater for patients with nephritic flares ($P < 0.00001$) with a relative risk of 27 (95% CI = 3.8 to 222).

By univariate analysis, the following clinical features at presentation were significantly associated with the risk of developing nephritic flares: male sex ($P = 0.002$), plasma creatinine higher than 1.5 mg/dl ($P = 0.0015$), arterial hypertension ($P = 0.0005$), number of extra-renal symptoms ($P = 0.01$), and hematocrit lower than 26% ($P = 0.001$). By multivariate analysis, only male sex ($P = 0.015$) and arterial hypertension ($P = 0.004$) were independent predictors of renal flares characterized by increased plasma creatinine. The relative risk of developing these nephritic flares was 4 for men (95% CI = 1.3 to 12.8) and 3.8 for patients with arterial hypertension at presentation (95% CI = 1.54 to 9.33).

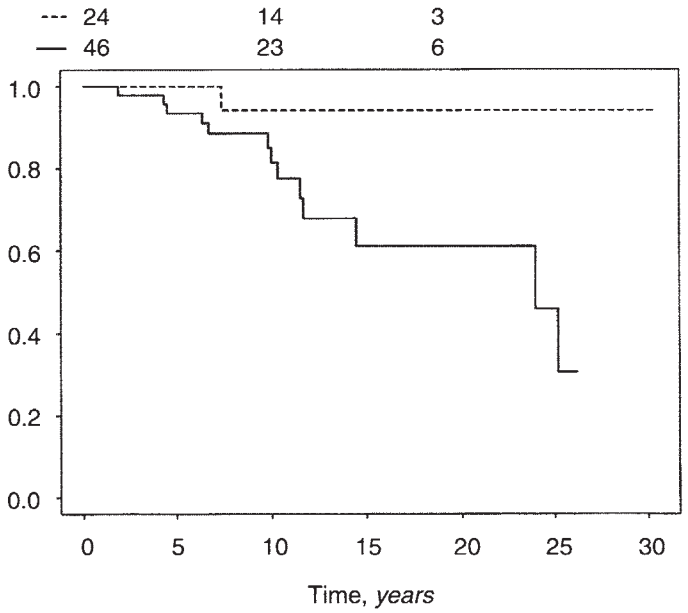

Fig. 2. *Probability of not reaching the end point (persistent doubling of plasma creatinine) of patients who had no renal flares (dashed line) and of patients who had renal flares of any type (solid line).* The difference between the two curves is statistically significant ($P = 0.03$). Numbers on the top indicate the number of patients at risk.

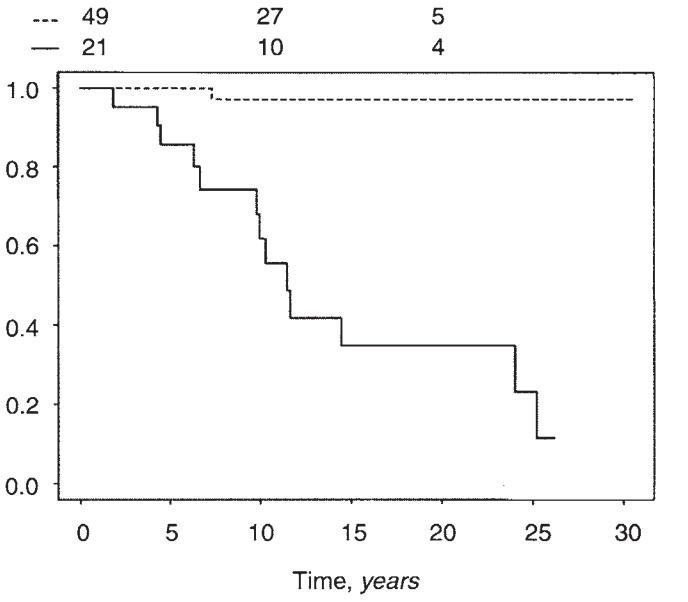

Fig. 3. *Probability of not reaching the end point (persistent doubling of plasma creatinine) of patients who had "nephritic flares" with a rapid increase in plasma creatinine (solid line) and of patients who either had no renal flares or "proteinuric flares" without changes in renal function (dashed line).* The difference between the two curves is statistically significant ($P = 0.00001$). Numbers on the top indicate the number of patients at risk.

Discussion

In this series, the outcomes for 70 Italian patients with lupus nephritis followed for a minimal period of five years in a single center were analyzed retrospectively. The extra-renal manifestations at presentation were similar to that reported by other authors [3, 29]. The patient survival rate was 100% at 10 years and 86% at 20 years, and the probability of not having a persistent doubling of plasma creatinine (the end point of the study) was 94% at five years, 85% at 10 years and 72% at 20 years. Therefore, most of the events occurred after the fifth year, which permitted an assessment of the long-term roles of prognostic factors, unlike most published studies where the fate of patients was heavily influenced by early deaths or renal failures [5, 6, 8–10, 12–15, 19].

We first evaluated the prognostic role of some clinical, biochemical and histological characteristics of the patients at presentation. When a multivariate analysis was done, only male sex and anemia were found to be associated with the risk of reaching the end point. It is well known that lupus nephritis has a worse prognosis in men than in women [16, 30]. Several studies have also detected the unfavorable prognostic significance of anemia in patients with lupus nephritis [9, 11, 14]. Instead, we did not confirm the prognostic role of elevated plasma creatinine at presentation reported by others [5, 6, 9–11, 14, 16, 17]. As pointed out by some investigators [7, 9, 10, 13] we could not find any correlation between the histological WHO class at presentation and the outcome. For our series, however, we excluded patients with already established severe renal failure. In addition, in our patients the duration of lupus nephritis before admission to our Unit was short, so that the increased plasma creatinine at presentation probably reflected a potentially reversible active renal disease rather than an irreversible chronic renal insufficiency. This hypothesis was confirmed by the small number of patients with a high chronicity index at the initial renal biopsy. On the other hand, all the studies that found a prognostic role of initial plasma creatinine [5, 6, 9–11, 14, 16, 17] had mean follow-ups of no more than five years. The studies with follow-ups of 10 years or more concluded that there is no association between initial plasma creatinine and the final outcome [7, 12, 31]. In particular, Esdaile et al [7], who used a time-dependent analytic approach, concluded that increased plasma creatinine at presentation may predict the outcome only for the first years of observation, but not after five or more years.

The long-term prognostic value of symptoms and signs at presentation is limited. In fact, the evolution of lupus nephritis is often unpredictable not only because of large interindividual variations, but also because the course of the disease may be variable in the same patient. Some patients who initially have a mild form of renal involvement may develop hectic activity, while other patients with initially severe disease may enter stable and complete remission after adequate therapy. It is also well known that a number of patients may have a transition from one histological class to another [32]. To the best of our knowledge, no study has investigated the prognostic value of renal flares in the long-term renal evolution of patients with lupus nephritis. In this study, we considered two types of renal flares, one characterized by an increase in proteinuria without renal dysfunction and the other characterized by a rapid increase in plasma creatinine. Patients who never had flares had a significantly greater number of stable and complete remissions than patients who did have renal flares. The relative risk of reaching the end point was also significantly lower for patients who never had flares. Surprisingly, no patient with the flares characterized by proteinuria alone eventually reached the end point. This does not necessarily mean that these patients will not have any deterioration of renal

function in the long-term. As a matter of fact, almost ⅓ of patients who eventually developed flares with an increase in plasma creatinine had only flares with change in proteinuria for several years. The relative risk of reaching the end point was 27 times greater in patients with the flares characterized by a rapid increase in plasma creatinine. The complete reversibility of renal dysfunction after treatment of a flare-up heralded a better prognosis. The unfavorable influence of renal exacerbations may be due to the fact that, in spite of therapy, glomerular injury produced by relapses of SLE may cause lesions that eventually lead to global or focal glomerulosclerosis [33]. This evolution might depend on the severity of the lesions caused by each flare as well as on the promptness and adequacy of the therapy instituted. Since the occurrence of renal flares with kidney dysfunction can heavily influence the outcome of lupus nephritis, it might be useful to predict which patient will be likely to have a renal flare-up. By multivariate analysis two variables were significantly associated with the risk of nephritic flares: male sex and arterial hypertension at presentation.

In summary, this study confirms the current opinion that the long-term prognosis of lupus nephritis has considerably improved in recent years. However, it is clear that the better the long-term prognosis, the weaker the prognostic significance of clinical characteristics at presentation. Therefore, it might be better to look at the activity of the disease during the follow-up to predict the renal outcome of lupus nephritis in the long-term. In this study, the occurrence of flares characterized by rapid increases in plasma creatinine was the strongest predictor of the eventual development of irreversible deterioration renal function. The latter event was more likely to occur in patients who did not respond promptly to therapy. It is thus recommended that all patients with lupus nephritis, particularly men and hypertensive patients, continue to be closely monitored in order to catch and treat early and vigorously any possible deterioration of renal function caused by flares of SLE activity. These data may indirectly support a therapeutic strategy based on an aggressive treatment of lupus exacerbation, while sparing corticosteroids and immunosuppressive agents in the quiescent period to prevent iatrogenic toxicity. This type of therapy has resulted in good patient and kidney survival for 20 years and longer in our patients with lupus nephritis.

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