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Original Article

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The long-term outcome of 93 patients with proliferative lupus nephritis

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Abstract

Background. Few data are available about the very long-term outcome of patients with proliferative lupus nephritis.

Methods. Ninety-three Italian patients with biopsy-proven proliferative lupus nephritis (15 with class III, 9 with class III + V, 64 with class IV and 5 with class IV + V) followed for a median follow-up of 15 years in a single renal unit were considered for this observational study. Patients were treated with an induction treatment consisting of high doses of corticosteroids plus immunosuppressive agents in the more severe cases. This treatment was repeated in the event of a renal flare. Then corticosteroids and immunosuppressive agents were reduced to the minimal effective dose for maintenance.

Results. Renal survival including death was 97% at 10 years and 82% at 20 years. At the last follow-up visit, 59 patients were in complete renal remission, 18 were in partial renal remission, four patients had chronic renal insufficiency, six had entered end-stage renal disease and six patients had died.

At multivariate analysis the lack of achievement of complete renal remission and the occurrence of nephritic flares were significantly correlated both with the risk of doubling plasma creatinine and death or dialysis. Those patients who entered complete renal remission had significantly less probability of developing nephritic flares.

Conclusion. The long-term prognosis of Caucasian patients with proliferative lupus nephritis may be better than usually thought. Favorable factors for good long-term outcome are the achievement of complete renal remission, the absence of nephritic flares and their complete reversibility after therapy.

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Keywords: immunosuppressive therapy; long-term renal survival; lupus nephritis

Introduction

Renal involvement is frequent in systemic lupus erythematosus (SLE) and may greatly influence the course of the disease. In general, the prognosis is more severe for patients with diffuse or focal proliferative glomerulonephritis while the course of pure membranous SLE nephritis is often considered to be more indolent [1].

There is general agreement that proliferative lupus nephritis deserves an aggressive treatment, particularly when patients present with increased serum creatinine and/or nephrotic proteinuria with high activity indices at renal biopsy [2]. Until recently, corticosteroids and intravenous pulses of cyclophosphamide have been the routine treatment for patients with proliferative lupus nephritis. This treatment appeared to improve the probabilities of remission in comparison to corticosteroids alone, even when corticosteroids were given at high doses by intravenous pulses. However, as such a strategy often brought with it severe side effects [3] the use of lower doses of intravenous cyclophosphamide followed by azathioprine began to be used as an alternative treatment. A multicentre randomized trial showed that the efficacy of this latter regimen was equivalent to treatment with high-dose intravenous cyclophosphamide. The risk of severe infections was halved with the new regimen but the difference was not statistically significant [4]. Another controlled trial compared intravenous cyclophosphamide pulses plus oral prednisone with intravenous pulses of methylprednisolone plus azathioprine. After a median follow-up of 5–7 years no difference in serum creatinine or proteinuria between the two groups was found [5].

There is little information about the long-term prognosis of patients with SLE proliferative nephritis.

Only a few studies have reported the outcome for patients followed for 5 years or more, and in most cases the number of patients was small. In this paper we report the long-term outcome of 93 patients with biopsy-proven proliferative lupus nephritis followed by a single centre for a median of 15 years and treated with a flexible strategy, mainly based on high-dose corticosteroids and oral cytotoxic agents for induction, followed by small doses of prednisone and azathioprine for maintenance [6]. In this cohort of patients we also evaluated the time-dependent predictive factors associated either with chronic renal insufficiency or with end-stage renal disease/death.

Subjects and methods

Participants

Of 194 patients with lupus nephritis referred to our renal unit from practitioners or from rheumatological or immunological units between January 1973 and December 2000, 101 Italian patients had an histological diagnosis of proliferative nephritis, class III or class IV [7] and a potential follow-up of at least 5 years. All the other patients but three had, at renal biopsy, different classes of lupus nephritis or a follow-up of <5 years. Three SLE patients admitted to our unit in the same period for nephritic (two patients) or nephrotic syndrome (one patient) were not submitted to renal biopsy due to low platelet count. Eight out of the 101 patients had a creatinine clearance lower than 20 ml/min at presentation and a chronicity index higher than 8 [2] at initial renal biopsy and were considered to have irreversible renal failure and were excluded from the study. At presentation, all the remaining 93 patients fit the diagnosis of SLE according to American College of Rheumatology criteria [8]. For the aims of this study, all the renal biopsies were reviewed and reclassified according to ISN/RNP classification [7]. Activity and chronicity indices were calculated according to the score proposed by Austin *et al.* [2].

Treatment

All patients were treated according to a flexible strategy, already described elsewhere [6,9]. The philosophy of such a strategy was to start with an induction treatment based on high-dose corticosteroids associated with an oral cytotoxic agent in the more severe cases or with azathioprine in milder cases. When the activity of the disease was quenched, the cytotoxic agent was replaced by azathioprine for maintenance, trying to reduce treatment to the minimal possible doses. In selected patients a cautious attempt of complete withdrawal was tried [10]. An induction treatment was started again in any cases of flares of activity [9].

Definitions

- The hard end point was defined by death or the need of chronic dialysis.
- For the other definitions we used those recently proposed by the Renal Subcommittee of Renal insufficiency of the American College of Rheumatology [11]:
- Renal insufficiency at presentation: serum creatinine >1.2 mg/dl and creatinine clearance lower than 75 ml/min.
- Nephrotic syndrome: proteinuria >3.5 g/24 h with plasma albumin < 3 g/dl.
- Non-nephrotic proteinuria: proteinuria between 0.21 and 3.5 g/24 h.
- Arterial hypertension: supine diastolic blood pressure >90 mmHg and/or systolic blood pressure >140 mmHg in three consecutive measurements.
- 'Nephritic flare': a sudden increase in plasma creatinine of at least 30% over the last value, associated with nephritic urinary sediment and increased proteinuria.
- 'Proteinuric flare': 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 doubled, if the patient already had nephrotic proteinuria.
- Chronic renal insufficiency: doubling of plasma creatinine lasting for at least 6 months with a value of plasma creatinine of at least 2 mg/dl and creatinine clearance ≤ 40 ml/min without any improvement over time.
- End-stage renal disease: the need of dialysis therapy.
- Complete renal remission: serum creatinine ≤1.2 mg/dl, and 25% increase of baseline creatinine clearance if abnormal, or stable value if normal at baseline, proteinuria <0.2 g/24 h, and inactive sediment defined as ≤5 red blood cells/high power field (hpf), ≤5 white blood cells/hpf and no cellular casts.
- Partial renal remission: proteinuria from 0.21 to 2 g/day and serum creatinine ≤1.2 mg/dl, and 25% increase of baseline creatinine clearance if abnormal, or stable value if normal at baseline.
- The creatinine clearance has been calculated according to Cockcroft and Gault.
- ECLAM (European Consensus Lupus Activity Measurement) score [12] was evaluated at presentation and at last observation (range 0–10).

Statistical methods

The statistical package S-Plus was used to analyse sample data. Means ± SDs were used for descriptive analysis. Since most of the variable distributions showed high non-normality, median and 25% to 75% interquartile range (IQR) were also calculated. Survival curves were drawn using the Kaplan–Meier estimate and compared using the log-rank test. Univariate and multivariate proportional hazards Cox regression analysis was used to investigate the prognostic value of continuous and binary (dichotomised) variables. At the univariate analysis, the following variables were tested: sex, age, months between the diagnosis of SLE and lupus nephritis, C3 an C4 complement fractions, anti-DNA antibody titres, white cell count, haematocrit, platelet count, aPL antibody positivity, serum albumin, serum creatinine, proteinuria, nephrotic syndrome, number of red blood cell count, arterial hypertension at diagnosis of lupus nephritis, activity and chronicity index, ECLAM score, treatment with aspirin, anti-malarials, Ace-inhibitors/ARB and the following time-dependent factors: persistence of

arterial hypertension, occurrence of complete renal remission and of nephritic flares, or of proteinuric flares. As statins were administered to a few patients only in recent years we could not evaluate their statistical power. For the multivariate analysis no automatic selection process was used, due to the limited size of the sample. All the variables that were significant at univariate analysis were included. After finding the independent predictors, also the variables that were not significant at univariate analysis were tested.

Relative risks and their 95% confidence intervals were derived, after fitting the Cox proportional hazard model, as the antilogarithm of the coefficient estimated for each covariate.

Results

Characteristics of the patients (Table 1)

Ninety-three Italian patients with biopsy-proven proliferative lupus nephritis (15 with class III, 9 with class III + V, 64 with class IV and 5 with class IV + V) and a minimal potential follow-up of at least 5 years were considered for this observational study. The median age at presentation of lupus nephritis was 27.3 years (IQR 21–33.4). Eight patients were males and 85 females. The median duration of SLE before the diagnosis of lupus nephritis was 1 month (IQR 0–29). SLE and lupus nephritis were diagnosed in 45 patients at the same time. The median duration between the diagnosis of lupus nephritis and the beginning of the therapy was 2 months (IQR 0.9–7.1).

At presentation of lupus nephritis 44 patients (47%) had renal insufficiency (median serum creatinine 1.6 mg/dl, (IQR 1.32–2.25 mg/dl); median creatinine clearance 43.9 ml/min, (IQR 33.0–57.8 ml/min) associated in 28 patients with nephrotic syndrome (median proteinuria 5.6 g/24 h; IQR 4.4–7.7 g/24 h) and with non-nephrotic proteinuria in the other 16 patients (median proteinuria 1.9 g/24 h; IQR 1.8–2.8 g/24 h). The remaining 49 patients (53%) had normal renal function, with nephrotic syndrome in 21 (median proteinuria 5.0 g/24 h, IQR 4.6–6.1 g/24 h) and non-nephrotic proteinuria (median 2.1 g/24 h, IQR 1.3–2.8/24 h) in 28 patients. All patients had microscopic haematuria (median number of erythrocytes 15/hpf IQR 7–40). Sixty patients had arterial hypertension.

C3 and C4 complement fractions were low, respectively, in 80 and 75 patients, 87 patients had positive anti-DNA antibodies and 16 had positive antiphospholipid antibodies. In 57 patients haematocrit was below 35%, in 13 patients platelet count was below 150 000/mmc, and in 20 patients white blood cell count was below 4000/mmc.

At renal biopsy the median value of activity and chronicity index were respectively 8 (IQR 5.0–10.5) and 2 (IQR 1–3). Fifty-four patients had been treated with ACE-inhibitors/ARB, 14 with aspirin and 27 with anti-malarials.

The following extra-renal manifestations of SLE at presentation of lupus nephritis were exhibited: arthritis in 69 patients (74.2%), skin involvement in 60 patients (64.5%), fever in 56 patients (60%), lymphoadenopathy in 18 patients (19,3%), serositis in 17 patients (18.3%), cerebritis in six patients (6.4%). The median ECLAM score was 6 (IQR 4–7).

Table 1. Clinical and histological characteristics at presentation of patients according to the initial therapeutical strategy

	Steroids (18 patients)	Cyclophosphamide/ Chlorambucil (55 patients)	Azathioprine (20 patients)
Serum creatinine (mg/dl)	1 (0.8–15)	1.3 (0.9–2.5)	1 (0.8–1.8)
Proteinuria (g/24 h)	3.4 (2–4.8)	5 (2.5–6)	3.9 (2.2–4.6)
Creatinine clearance (ml/min)	74 (58–98)	69 (48.9–91)	71 (34–97)
Urinary erythrocyte (n°/hpf)	15 (7–40)	20 (8–40)	15 (5–40)
C3 (mg/dl)	52 (35–90)	53 (45–66)	50 (50–60)
C4 (mg/dl)	10.5 (7–2.5)	10 (5–14)	10.5 (5–19)
ECLAM score	5 (4–7)	6 (5–8)	5.5 (4–7)
Activity index	6 (4–10)	8 (6–11)	6.5 (4.2–9.7)
Chronicity index	1 (1–3)	2 (0–3)	2 (1–3)
Haematocrit (%)	35 (30–40)	32 (29–36)	33 (27.5–37)
Arterial hypertension (% of patients)	38%	69%	75%

If not otherwise specified, the numbers are the median values and (interquartile ranges).

Therapy

Induction treatment. Eighteen patients were treated with oral prednisone 1–2 mg/kg per day in a single morning administration for 1 month then gradually reduced to the maintenance. The other 75 patients started therapy with a methylprednisolone pulse of 0.5–1 g/day for three consecutive days followed by oral prednisone 0.5–1 mg/kg/day for 1–2 months then gradually reduced to the maintenance. In 75 patients (81%) with plasma creatinine higher than 1.2 mg/dl and/or proteinuria higher than 5 g/day and or activity index >5 an immunosuppressive agent was added to the steroids: in 45 patients cyclophosphamide 1.5–2 mg/kg/day was given for a median period of 3 months (IQR 2–4), in 10 patients chlorambucil 0.15–0.2 mg/kg/day for a median period of 3 months (IQR 2–3.8), and 20 patients azathioprine 2 mg/kg/day for a median period of 13.5 months (IQR 7.3–28). Such an induction therapy was repeated in the case of renal flares [9].

The clinical characteristics of patients treated with steroids alone, steroids plus n cyclophosphamide/chlorambucil and steroids plus azathioprine are reported in Table 1.

Maintenance. Depending on the improvement of renal and extra-renal signs and symptoms, prednisone was progressively tapered until reaching a dose of

10 mg per day. A further reduction was attempted in patients who reached a complete *renal* remission. After induction, cyclophosphamide and chlorambucil were replaced with azathioprine in 25 patients (1–1.5 mg/kg/day) for a median period of 14 months (IQR 8–35) with cyclosporine in three patients and with mycophenolate mofetil in two patients, while the other 25 continued with prednisone alone. Patients who were given azathioprine for induction continued with azathioprine for maintenance at doses ranging between 1.0 and 1.5 mg/kg/day. In 32 patients both corticosteroids and immunosuppressive agents were completely withdrawn. Fifteen patients (Group 1) never developed lupus flares. The other 17 patients (Group 2) developed lupus flares in mean 55.8 + 58.3 months after stopping therapy and were again treated. At the last follow-up (184.9 + 81.4 months after withdrawal of therapy) 12 patients from group 1 were in complete remission, two patients had mild proteinuria and one patient died. In group 2, one patient died, 14 patients were in complete remission, one patient had mild proteinuria and in another patient serum creatinine doubled [10].

Outcome

Patients were followed for a median period of 181 months (IQR 97–251 months). A complete *renal* remission was attained in 76 (82%) patients after a median follow-up of 14 months (IQR 7.4–43.2) from the beginning of the induction therapy. Among the clinical and histological characteristics at presentation, the only predictors of complete renal remission were age at study entry (mean 29.3 + 10.1 years in patients who attained complete renal remission *vs* 23.9 + 8.45 years in patients who did not $P = 0.01$) and the longer duration of systemic lupus before the diagnosis of lupus nephritis (mean 29.5 + 49.5 months in patients who attained complete renal remission *vs* 5 + 11.4 months in patients who did not $P = 0.04$).

Nephritic flares occurred in 28 patients (15 patients one flare, 7 patients two flares and 6 patients three or more flares) after a median follow-up of 47 months (IQR 12–114) from the beginning of the induction therapy. Proteinuric flares occurred in 46 patients (21 patients one flare, 12 patients two flares, 13 patients three or more flares) after a median period of 50.1 months (IQR 32.3–73) from the beginning of the induction therapy. Fourteen patients had both proteinuric and nephritic flares. Taken together, 60 patients out of 93 (64%) developed at least one renal flare during a 15-year follow-up.

Chronic renal insufficiency developed in 14 patients (15%) after a median follow-up of 141.2 months (IQR 96.6–232.0) The risk of developing chronic renal insufficiency was 10% at 10 years, 14% at 15 years and 17% at 20 years (Figure 1). Among the 14 patients who developed chronic renal insufficiency, six reached end-stage renal disease 154 months (IQR 118–175) after the diagnosis of lupus nephritis.

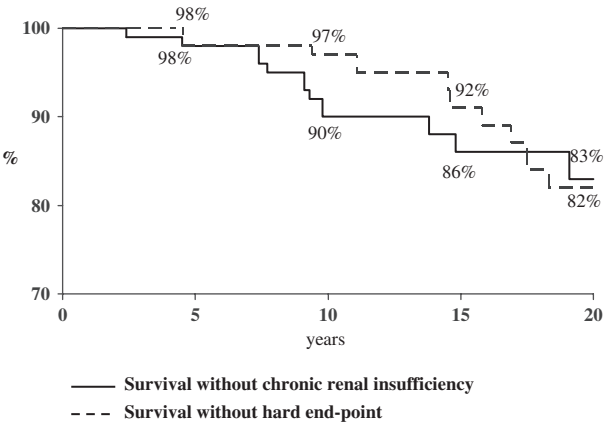

Fig. 1. Survival without doubling serum creatinine and survival without dialysis and/or death.

Six patients died after a median follow-up of 231 months (IQR 205–325). Of them, two were in partial remission and four had chronic renal insufficiency. The patient survival was 100% at 15 years and 92% at 20 years. The latest report of the Statistical Italian Institute (ISTAT) gives a life expectancy at 20 years of 97% for Italian women aged 28 years. The causes of deaths were malignant neoplasia in two patients, cerebral haemorrhage in two patients, myocardial infarct in one patient and cachexia in the last patient. Three other patients died after the beginning of chronic dialysis. Altogether 12 patients, of whom 10 of the 14 with chronic renal insufficiency, reached the hard end-point (death and/or end-stage renal disease) (Figure 1).

At the last observation, 59 patients (63,4%) were in complete renal remission, 18 (19,3%) were in partial renal remission, four (4.5%) had chronic renal insufficiency, six (6.4%) entered end-stage renal disease and six patients (6.4%) died. The median ECLAM score at last observation was 1 (IQR 0–1). The renal survival, including death, was 97% at 10 years, 92% at 15 years and 82% at 20 years (Figure 1).

When we divided our patients into two survival cohorts, those presenting with lupus nephritis between 1973 and 1986 (41 patients) and those diagnosed between 1987 and 2000 (51 patients), no differences in survival between the two cohorts emerged for survival without ESRD or death. The probability of doubling serum creatinine was significantly lower in patients diagnosed between 1987 and 2000 (98% at 10 years) in comparison to those diagnosed between 1973 and 1986 (85% at 10 years, $P = 0.00012$).

The main side-effects and complications are the following: infections requiring hospitalization, 15 patients (16%); herpes zoster, 16 patients (17%); minor infections, two patients (2.1%); ovarian failure (defined as the occurrence of menopause before 40 years), 10 patients (11%); bone aseptic necrosis, 5 patients (5.3%); osteoporosis, 12 patients (13%); myocardial infarction and/or cerebral thrombosis, 12 patients (13%). Four malignancies occurred: one

Table 2. Characteristics of patients and their prognostic value on the development of chronic renal insufficiency (doubling of serum creatinine)

	Characteristics of patients at presentation			
	All 93 patients	79 pts with normal renal function at the last observation	14 pts with doubling serum creatinine at the last observation	P^*
Age (years) median (IQR)	27.3 (21; 33.7)	27.26 (21.4;33.7)	27 (18.93;29.24)	ns
Sex (male/female)	8/85	5/74	3/11	ns
Months between SLE and LN diagnosis median (IQR)	1 (0; 29)	2 (0;32)	0 (0;2.8)	ns
Serum creat. (mg/dl) median (IQR)	1.1 (0.8;1.6)	1 (0.8;1.5)	1.65 (1.1;2.2)	ns
Serum creat. > 1.5 mg/dl n° of pts	27	18	9	0.01
GFR (ml/min) median (IQR)	69 (47.3; 90.4)	72.5 (53.2;100)	50.6 (34.8;75)	ns
Proteinuria g/24 h median (IQR)	4 (2.3;5.4)	3.99 (2.3;5.5)	4 (2.5;4.7)	ns
Urinary RBCn°/hpf median (IQR)	15 (7;40)	15 (5;40)	22.5 (15; 40)	ns
Ser.albumin gr/dl median (IQR)	2.8 (2.3; 3.5)	2.9 (2.4;3.5)	2.4 (2.3; 3.07)	ns
Anti-DNA (pos/neg)	82/6	69/5	13/1	ns
aPL (pos/neg)	14/63	11/54	3/9	ns
C3 mg/dl median (IQR)	52 (45;64)	52 (45;64)	51.5 (50;59)	ns
C4 mg/dl median (IQR)	10 (5;14)	11 (6;14.5)	7 (5;12)	ns
White cells/mmc median (IQR)	5600 (4000;7225)	5550 (3975;6750)	6050 (4700;7850)	ns
Hematocrit% median (IQR)	33 (29;37)	33.4 (30;37)	29.5 (25;31.7)	0.04
Platelets/mmc median (IQR)	239000 (168000;305750)	241000 (166750;301250)	224500 (181000;308250)	ns
ECLAM	6 (4;7)	6 (4;7)	6.5 (5.2;7)	ns
Hypertension (yes/no)	60/32	47/31	13/1	0.04
Activity index median (IQR)	8 (5;10.5)	8 (5;10)	7.5 (5.2;11.7)	ns
Chronicity index median (IQR)	2 (1; 3)	2 (1;3)	2(0.25;3.7)	ns
	Supportive therapy during the follow-up			
ACE-inhibitors/ARB (yes/no)	54/39	44/35	10/4	ns
Aspirin (yes/no)	14/79	10/69	4/10	ns
Anti-malarials (yes/no)	27/66	26/53	1/13	ns

IQR, interquartile range; LN, lupus nephrits; Creat., creatinine; GFR, glomerular filtration rate; RBC, red blood cells; hpf, high power field.
*P value refers 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).

lung cancer, one thyroid cancer, one breast cancer and one uterine cancer.

Predictors of outcome

The renal survival including death was 100% at 10 and at 15 years and 85% at 20 years for patients with class III and 96% at 10 years, 89% at 15 years and 82% at 20 years in patients with class IV lupus nephritis. There was no significant difference in the renal or patient survival at any time point between patients with class III and patients with class IV lupus nephritis at initial biopsy.

Among the clinical characteristics at presentation only serum creatinine >1.5 mg/dl ($P = 0.01$), low haematocrit ($P = 0.04$) and arterial hypertension ($P = 0.01$) were predictive of the development of the doubling of serum creatinine (Table 2).

The risk of doubling serum creatinine was related to the persistence of arterial hypertension ($P = 0.04$), the lack of achievement of complete renal remission ($P = 0.0000006$) (Figure 2) and the development of nephritic flares ($P = 0.000005$) (Figure 3). Chronic renal insufficiency developed in 13 out of the 28 patients (46%) in whom nephritic flares occurred. The number of nephritic flares was also significantly correlated

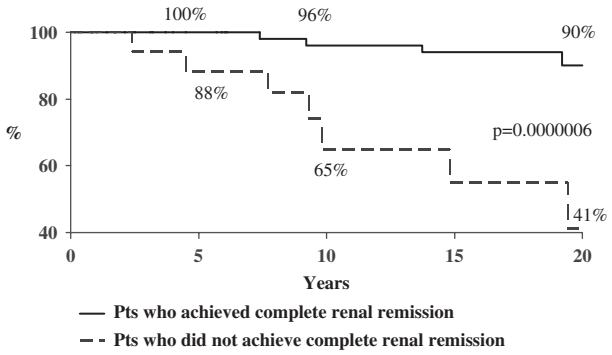

Fig. 2. Survival without doubling serum creatinine in patients who achieved and in those who did not achieve complete remission. Pts, patients.

with the development of chronic renal insufficiency. Of the 13 patients who had more than one nephritic flare, 10 developed chronic renal insufficiency and only three maintained normal renal function, while of the 15 patients with one nephritic flare, only three doubled serum creatinine ($P = 0.0001$). The response to therapy was assessed at 3 months. Serum creatinine returned to the basal value in 77% of patients who eventually maintained normal renal function and in 16% of patients who developed chronic renal

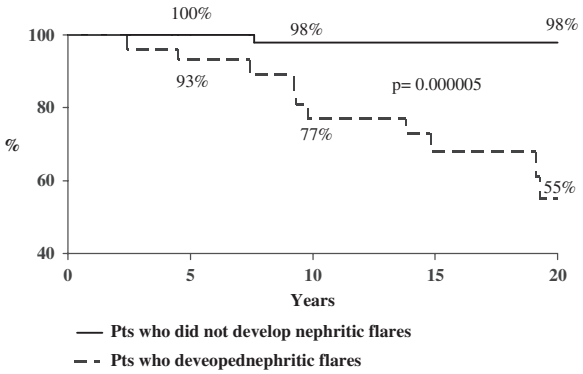

Fig. 3. Survival without doubling serum creatinine in patients who developed and in those who did not develop nephritic flares.

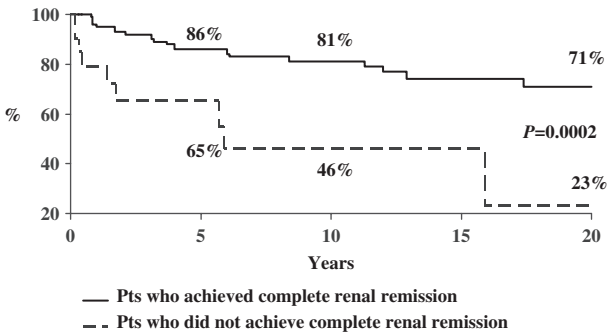

Fig. 4. Probability of not developing nephritic flares in patients who achieved or not complete renal remission.

insufficiency ($P = 0.0001$). Patients who reached complete renal remission had significantly lower probability of developing nephritic flares (Figure 4). At 20 years, the probability of survival without nephritic flares was 71% in patients who reached complete renal remission and 23% in patients who never reached complete renal remission ($P = 0.0002$).

At multivariate analysis, the lack of achievement of complete renal remission ($P = 0.01$) and the development of nephritic flares ($P = 0.01$) were the only independent predictors of development of chronic renal insufficiency. The lack of achievement of complete renal remission increased the risk of chronic renal insufficiency by a factor of 4.3 (CI 1.4–13.4). Nephritic flares increased the risk of development of chronic renal insufficiency by a factor of 13.8 (CI 1.7–113).

Among the clinical characteristics at presentation, only the chronicity index ($P = 0.04$) was predictive of end-stage renal disease and/or death (Table 3). Among the time-dependent risk factors, the development of the hard end-point was significantly correlated with the lack of achievement of complete renal remission ($P = 0.002$) and with nephritic flares ($P = 0.008$).

Discussion

The prognosis of lupus nephritis has improved over the years. By reviewing the published literature, Cameron

Table 3. Prognostic power of the characteristic of the patients to predict the development of the hard end-point (end-stage renal disease or deaths)

	Characteristics of patients at presentation		
	Patients alive with functioning kidney	Patients in chronic dialysis or deceased	*P*
Age (years) median (IQR)	26.7 (21;33.7)	27.8 (21.1;30.6)	ns
Sex (male/female)	5/76	3/9	ns
Months between SLE and LN diagnosis median (IQR)	1(0;29.1)	1 (0;3.9)	ns
Serum creat. (mg/dl) median (IQR)	1 (0.8;1.5)	1.8 (1.5;2.4)	ns
GFR (ml/min) median (IQR)	72.5 (55.2;99)	38.8 (34; 69.9)	ns
Proteinuria (g/24 h) median (IQR)	4 (2.6;5.4)	2.7 (1.3;4.5)	ns
Urinary RBC n°/hpf) median (IQR)	15 (5;40)	35 (15; 40)	ns
Serum albumin (g/dl) median (IQR)	2.9 (2.4;3.5)	2.6 (2.1;3.1)	Ns
Anti-DNA (pos/neg)	71/6	11/0	ns
aPL (pos/neg)	10/57	4/6	0.07
C3 mg/dl median (IQR)	52.5(45;64)	50 (50;57)	ns
C4 mg/dl median (IQR)	10 (6;14)	10 (5;12.3)	ns
White cells/mmc median (IQR)	5600 (3900;6800)	6500 (4800;7700)	ns
Hematocritt% median (IQR)	33 (29;37)	31.4 (27.9;35.3)	ns
Platelets/mmc median (IQR)	241000 (167250;303750)	224500 (192000;317000)	ns
ECLAM score	6 (4;7)	6.5 (5;7)	ns
Hypertension yes/no	51/29	9/3	ns
Activity index median (IQR)	8 (5;10)	8.5 (6;12)	ns
Chronicity index median (IQR)	2 (0.5;3)	2.5(1;4.75)	0.04
	Supportive therapy during the follow-up		
ACE-inhibithors (yes/no)	46/35	8/4	ns
Aspirin (yes/no)	11/70	3/9	ns
Anti-malarials (yes/no)	26/55	1/11	ns

IQR, interquartile range; LN, lupus nephrits; Creat, creatinine; GFR, glomerular filtration rate; RBC, red blood cells; hpf, high power field.
**P* value refers 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).

[13] found that life expectancy at 5 years increased from 44% in the period 1953–1969 to 82% in the period 1980–1995. Derksen *et al*. [14] reported a mortality of 11,2% after a mean follow-up of 53 months in 56 patients with biopsy-proven lupus nephritis, of whom 38 with proliferative lupus nephritis. Nossent *et al*. [15] reported a survival of 82% at 15 years in 26 patients with proliferative lupus nephritis. Few papers have reported the long-term renal outcome in patients with lupus nephritis [13,16,17]. With one exception [17], in those reports not only patients with proliferative glomerulonephritis, but also patients with other subtypes of lupus nephritis were included. In this study we selected patients with biopsy-proven type III or type IV lupus nephritis and with a potential follow-up of at least 5 years. The only criterion of exclusion was the presence of irreversible renal failure, defined by a creatinine clearance lower than 20 ml/min associated with an elevated chronicity index at renal biopsy. We were able to recruit 93 patients who were followed for a median of 15 years, the longest follow-up for such a typology of patients, to the best of our knowledge. About half of our patients had some degree of renal dysfunction at presentation. The expected patient survival at 20 years was 92%. The renal survival, including death, was 97% at 10 years and 82% at 20 years. These data show that the renal prognosis of proliferative lupus nephritis may be considerably better than generally estimated, at least in Caucasian patients.

A number of factors may account for this good prognosis. The choice of the therapeutic strategy may have had an important role. Two main causes of renal failure or death in lupus nephritis patients are an over-treatment which causes severe and life-threatening morbidity or an under-treatment which causes a silent, progressive kidney dysfunction and other extra-renal complications of SLE. In an attempt to avoid either of these risk factors we have used since the early 70s an aggressive, but relatively short treatment for induction and flares, while reducing to the minimal, effective dosage corticosteroids and immunosuppressive drugs whenever the activity of lupus nephritis was quenched. However, even this strategy may lead to over- or under-treatment, as assessing whether lupus nephritis is active or inactive is not always easy. To minimize this risk we have created a small task force of nephrologists dedicated to the follow-up of SLE patients. Moreover, patients were asked to come regularly to our unit for laboratory and clinical check-up, this program being made possible by the fact that until recently the laboratory tests and the clinical visits in hospital were free of charge in Italy. Another point of paramount importance was the fact that doctors following SLE patients were available by phone for any problem or query of the patient. Patients who did not present at regular visits were interviewed by phone in order to check their adherence to treatment. This strict surveillance probably allowed a prompt diagnosis and treatment and probably reduced the impact of another important risk factor for SLE patients, poor compliance. However, we cannot know whether such a therapeutical policy may also provide satisfactory results in other populations at a higher risk (i.e. African American, Hispanic) or in other settings where it is difficult to organize a task force of nephrologists devoted to lupus nephritis.

In this series the risk of death or end-stage renal failure was particularly elevated in the 14 patients who showed a persistent doubling of serum creatinine. Four of them died, six developed end-stage renal failure and three of them eventually died after starting chronic dialysis. The other two deaths occurred many years after admission in patients with partial remission. While the risk of renal failure in patients with increased serum creatinine speaks for itself, the unfavourable impact of renal dysfunction on patient survival is not unexpected in view of the recent evidence showing an increased risk of cardiovascular disease and other life-threatening complications in patients with renal insufficiency [18].

The risk of developing renal insufficiency was higher in patients who presented with serum creatinine higher than 1.5 mg/dl and/or hypertension, similarly to that which was reported by other investigators [2]. We also found a prognostic role for anaemia, a risk factor which was already pointed out by Austin *et al*. [2] and confirmed in our previous studies [9]. The available data do not explain whether anaemia simply reflected the association with renal dysfunction or actually represented an independent risk factor. However, treating anaemia may be advisable in SLE patients, also taking into account recent data showing that anaemia may be considered as a risk factor for cardiovascular disease [19]. Among the clinical and histological characteristics at presentation, the only significant risk factor for end-stage renal failure or death was a high chronicity index at initial renal biopsy. The prognostic role of this parameter has been evaluated by previous analyses in different ways. Some investigators reported that chronicity index represented a significant risk factor, [1,2] while others did not [20]. It is likely that those results were influenced by the differing severity of chronic lesions in different series. At any rate, there is little doubt that diffuse interstitial fibrosis, tubular atrophy and glomerular sclerosis are associated with a poor outcome, emphasizing the importance of an early diagnosis and treatment of SLE nephritis.

The analysis of time-dependent variables showed that two factors were significantly associated with the risk of developing renal insufficiency or hard end-points, i.e. the lack of complete renal remission and the occurrence of nephritic flares. Recent papers have pointed out the importance of complete remission in preventing the development of renal insufficiency [4]. The deleterious role of nephritic flares has been already demonstrated by us [9] and then confirmed by other investigators. The present data confirm our previous results and underline for the first time the importance of the achievement of complete renal remission in preventing the development of nephritic flares.

Our data also show that the risk of renal function deterioration is significantly higher in patients who experienced two or more flares than in patients with a single flare. Taken together, these data show the importance of quenching the renal activity of SLE. On the other hand, a protracted immunosuppressive therapy is likely to render SLE patients more susceptible to invalidating and even life-threatening side-effects. To control flares while avoiding a vigorous immunosuppressive therapy in the long term, we limited an aggressive treatment to established flares and submitted the patients to frequent clinical and lab monitoring to identify renal activity as soon as possible.

Most patients reached complete renal remission of renal disease. This happened after a median period of 14 months, a time similar to that observed in other series using different therapeutical schedules [4]. As already pointed out, we found that serum creatinine improved soon after beginning induction therapy, while the recovery of proteinuria occurred later. We decided not to increase induction or maintenance therapy to accelerate the remission of proteinuria in order not to increase the risk of iatrogenic morbidity. It is difficult to know whether a more aggressive therapy would have resulted in an earlier remission of proteinuria or an increased rate of severe side effects. At any rate, we continued our policy, having observed a high rate of complete renal remission.

During this long-term follow-up, about 30% of patients developed at least one nephritic flare which required further vigorous treatment. As mentioned above, patients who developed flares had a higher probability of developing renal insufficiency. On the other hand, most patients who completely recovered after treatment did not develop chronic renal insufficiency. This would mean that rather than trying to prevent flares with too aggressive a therapy, that may be associated with severe and life-threatening side effects, it might be better to reduce the doses of corticosteroids and immunosuppressive drugs for maintenance, while implementing clinical surveillance and being ready to increase treatment whenever signs of activity appear. In our experience such a strategy resulted in relatively few complications and also in a low mortality.

In conclusion, the retrospective analysis of this series shows that the long-term prognosis of Caucasian patients with SLE proliferative nephritis may be better than generally thought, if patients are referred to nephrologists before irreversible renal damage has already set in. We feel that treatment of lupus nephritis should be flexible so as to avoid the risks of over- or under-immunosuppression. Incomplete recovery from renal flares being an important risk factor for progression, we strongly recommend that patients are regularly followed by well-trained physicians and that flares are treated promptly and vigorously until serum creatinine returns to baseline values. On the other hand, to minimize iatrogenic morbidity, the doses of steroids and immunosuppressive agents should be slowly reduced to the minimal effective dosage in patients with inactive disease.

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