Renal Outcome in Patients with Lupus Nephritis Using a Steroid-free Regimen of Monthly Intravenous Cyclophosphamide: A Prospective Observational Study

REBECCA FISCHER-BETZ, GAMAL CHEHAB, OLIVER SANDER, STEFAN VORDENBÄUMEN, ADINA VOICULESCU, RALPH BRINKS, and MATTHIAS SCHNEIDER

ABSTRACT. **Objective**. Intravenous cyclophosphamide (IV CYC) in combination with high doses of corticosteroids is considered the "gold standard" of therapy for lupus nephritis (LN). However, the optimal dose of corticosteroids needed has not been defined. We evaluated the efficacy of a monotherapy with IV CYC in patients with a first episode of LN (duration ≤ 6 months).
Methods. Forty patients with LN received IV CYC (12 pulses). Prednisone alone was administered and dose-adjusted to control extrarenal manifestations. Response after 24 months was defined as normalization of creatinine level, inactive urinary sediment, and proteinuria ≤ 0.2 g/day [complete response (CR)] or ≤ 0.5 g/day [partial response (PR)].
Results. CR was achieved in 25 (62.5%) and PR in 8 (20%) patients. Mean starting dose of prednisone was 23.9 ± 23.8 mg/day. In a posthoc analysis, we separately analyzed patients initially treated with prednisone doses ≥ 20 mg/day (Group A, n = 19) or < 20 mg/day (Group B, n = 21). CR was achieved in 52.6% (Group A) versus 71.4% (Group B; p = 0.37); and PR in 26.3% versus 14.3%, respectively (p = 0.58). During longterm followup (10.4 ± 3.1 yrs), 37.8% experienced a renal flare. Thirty patients (81%) still have normal renal function. Renal outcome was irrespective of initial prednisone doses (p = 0.46, Pearson chi-square test of independence).
Conclusion. Our rates of CR and PR and longterm outcomes were comparable with rates after treatment with a combination of IV CYC with high doses of corticosteroids. These data warrant randomized controlled trials evaluating different doses of corticosteroids in LN. (J Rheumatol First Release Sept 15 2012; doi:10.3899/jrheum.120537)

Key Indexing Terms:
LUPUS NEPHRITIS   TREATMENT   CORTICOSTEROIDS   PROGNOSIS

Nephritis is a common, serious manifestation of systemic lupus erythematosus (SLE)[1]. In 10%–30% of such patients, the kidney disorder progresses to endstage renal disease (ESRD) within 15 years of diagnosis[1,2,3,4]. Intravenous cyclophosphamide (IV CYC) is widely used as an effective but also toxic regimen that enables a high rate of disease remission and preserves kidney function[5,6,7,8]. Therapeutic strategies to reduce the toxicity of IV CYC have shown similar efficacy compared with the traditional US National Institutes of Health (NIH) IV CYC regimen[9,10]. All regimens include moderate to high doses of oral or intravenous corticosteroids (GC). However, the optimal GC dose needed for successful induction treatment has not been ascertained in randomized studies. GC themselves are known to be associated with severe side effects and contribute to about 25% of longterm damage in SLE[11,12]. In addition, the majority of studies report that the development of cardiovascular complications is associated with GC therapy[13,14]. Recent guidelines confirm the lack of evidence from randomized trials to support any particular regimen of GC use in either the induction or maintenance of lupus nephritis (LN)[15,16]. Thus, controversy remains over the optimal use of GC in terms of their effects on disease activity, clinical outcome, and/or associated toxicity.

Risk stratification allows identification of patients at lower risk for renal dysfunction, for whom less aggressive therapy is likely to be beneficial. For example, prompt diagnosis after the onset of nephritis and subsequent initiation of appropriate therapy is associated with improved outcomes regardless of the histologic subclass[17,18]. We hypothesized that in LN that is diagnosed early, high GC doses do not have significant clinical effect concerning the response to induction treatment and longterm renal outcome. Thus, the rationale of our study design was to avoid as much GC as

possible. We therefore decided to refrain from use of not only oral GC but also methylprednisolone pulses. We prospectively studied the outcome of patients with LN who were treated with IV CYC and GC doses solely adapted to extrarenal disease activity.

MATERIALS AND METHODS

Patients. Patients with SLE according to the American College of Rheumatology (ACR) revised criteria[19] and a first episode of LN (duration ≤ 6 months) were eligible for this study. Disease onset was defined as the time the patient fulfilled the ACR criteria for SLE. Disease duration was defined as the period from disease onset to the time of the baseline examination. The time of onset of nephritis was defined as the first clinically evident renal disease with proteinuria (> 0.5 g/day) and hematuria [> 5 dysmorphic red blood cells (RBC)/hpf]. Patients with severe extrarenal lupus [active cerebral lupus, severe hemolytic anemia (hemoglobin < 7 mg/dl), thrombocytopenia (< 50,000/mm^3), or leukopenia (< 1000/mm^3)] were excluded, because they received methylprednisolone pulse treatment. In addition we excluded those with a relapse of LN, patients with liver disease, and pregnant patients. Renal biopsy specimens were assessed by immunofluorescence and light microscopy and categorized according to the 1982 World Health Organization classification[20].

Immunosuppressive treatment protocol. All patients received 12 IV CYC pulses over a period of 24 months (6 monthly pulses followed by 6 quarterly pulses). The initial CYC dose was 0.5 g/m^2 body surface area; subsequent doses were increased by 250 mg according to the white blood cell (WBC) count nadir measured on Day 14, with a maximum of 1500 mg per pulse. In addition, all patients received mesna (sodium-2-mercaptoethane sulfonate) to prevent hemorrhagic cystitis. Hypertension was treated initially with angiotensin-converting enzyme inhibitors, unless contraindicated. The use and dose of prednisone was based solely on the presence of mild to moderate extrarenal SLE manifestations, with subsequent dose tapering based on extrarenal activity as considered necessary by the treating physician. No additional methylprednisolone pulse therapy was administered in any patient for induction of remission of LN.

Patients were evaluated monthly within the first 6 months and quarterly thereafter. At each visit, a complete physical examination was carried out including blood pressure as well as routine laboratory testing [blood count, urinalysis, 24-h urinary protein, serum creatinine, creatinine clearance rate, serum complement component 3 (C3) level, and anti-dsDNA antibody]. Disease activity was assessed using the Systemic Lupus Activity Measure (SLAM)[21]. Accumulated organ damage was measured according to the Systemic Lupus International Collaborating Clinics damage index (SLICC/ACR-DI)[22]. Adverse events (e.g., infections) were recorded.

The study was approved by the local ethics committee of the University of Duesseldorf and written informed consent was obtained from all patients.

Study endpoints. Complete response (CR) after 24 months (12 pulses of IV CYC treatment) was defined as proteinuria < 0.2 g/day together with inactive urinary sediment (≤ 10 RBC/µl, ≤ 10 WBC/µl, no cellular casts) and normalization of creatinine level for at least 3 months. Partial response (PR) was defined as proteinuria ≤ 0.5 g/day together with inactive urinary sediment and normalization of creatinine level for at least 3 months. Patients who did not meet these criteria were regarded as nonresponders. Renal flares during longterm followup were defined as persistent increase of proteinuria (≥ 500 mg/day) together with recurrence of active urinary sediment (increased hematuria with or without reappearance of cellular casts) and/or increase of serum creatinine (≥ 25%) due to active disease, which required more intense immunosuppressive therapy.

Statistical analysis. All statistical tests were performed with the R software version 2.12 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). Descriptive statistics are reported as means ± SD, ranges, frequencies, or proportions as appropriate. The numbers (per-

centage) of responders and nonresponders were calculated for each factor, overall and by treatment group (prednisone < or ≥ 20 mg/day). Differences among study groups were analyzed by tests of equal proportions, Student's t tests, and Pearson's chi-square test of independence. Differences were considered statistically significant when 2-sided p values were < 0.05. Time to event analysis was performed according to the Kaplan-Meier method.

RESULTS

Baseline data and treatment. Between February 1995 and December 2004, 67 patients with SLE were diagnosed with active LN at the Department of Rheumatology. Twenty-six patients were not eligible for our study (19 had previously been treated for LN, 2 were pregnant, and 6 were critically ill with severe multiorgan involvement). A total of 41 patients met our inclusion criteria. One patient developed toxic hepatopathy after 2 IV CYC treatments and was therefore not included in the analysis. The remaining 40 patients were all white (33 women, 7 men), had a mean age of 29.7 ± 10.1 years, and had a mean SLE duration of 3.5 ± 2.8 years. Three (7.5%) presented with renal impairment (serum creatinine > 1.2 mg/dl) and 20 (50%) presented with a 24-hour urinary protein ≥ 2.5 g. Seven patients had previously been treated with azathioprine and 1 with cyclosporine. In 38 patients, the type of LN was verified by renal biopsy; in the remaining 3 patients no biopsy could be performed because of coagulation abnormalities. Baseline clinical and laboratory data are outlined in Table 1.

Response after 24 months. All patients completed the entire course of therapy with statistically significant reductions from baseline of SLAM scores, hemoglobin, proteinuria,

Table 1. Characteristics of all patients with SLE at baseline. Results are mean ± SD or n (%).

Characteristic	Patients, n = 40
Female	33 (82.5)
Age, yrs	29.7 ± 10.1
Duration of SLE, yrs	3.5 ± 2.8
SLAM	9.6 ± 3.6 (5–21)
SLICC	0.3 ± 0.6 (0.0–2.0)
Systolic blood pressure > 140 mm Hg	7 (17.5)
Diastolic blood pressure > 90 mm Hg	8 (20)
Serum creatinine, mg/dl	0.9 ± 0.3 (0.5–2.1)
24 h urinary protein, mg	3321 ± 2531
Hemoglobin, mg/dl	10.9 ± 1.6
C3, mg/dl (90–180)	56.2 ± 20.8
Anti-dsDNA, IU/ml (< 80)	243 ± 260
WHO class nephritis, n = 38	
No. patients (%)	
Class III	17 (43.6)
Class IV	19 (48.7)
Class V	2 (5.1)
Prednisone dosage, mg/day	23.9 ± 23.8
Hydroxychloroquine treatment	15 (37.5)

SLAM: Systemic Lupus Activity Measure; SLICC: Systemic Lupus International Collaborating Clinics Damage Index; WHO: World Health Organization; SLE: systemic lupus erythematosus.

complement, and anti-dsDNA levels (Table 2). After 24 months, 25 patients (62.5%) met the criteria for CR and 8 (20%) for PR. Baseline data for complete and partial responders were comparable (Table 3). The group that achieved CR comprised fewer patients with 24-h urinary protein ≥ 2.5 g at baseline (40% vs 87.5%); however, this difference did not reach statistical significance (p = 0.053; Table 3).

Outcome in patients treated with different prednisone doses. The mean daily starting dose of prednisone was 23.9 ± 23.8 mg/day. To investigate any prednisone effect, we performed a subgroup analysis, comparing patients who had been treated with prednisone ≥ 20 mg/day at baseline [high-dose: 21 patients (52.5%)] or prednisone < 20 mg/day [low-dose: 19 patients (47.5%); Table 4]. As expected, patients in the high-dose group had significantly higher SLAM scores at base-line. These patients experienced arthritis and serositis more often, had significantly lower hemoglobin, and had lower levels of complement C3 (Table 4). The mean cumulative dose of prednisone equivalents after induction treatment (Week 24) was 3.23 ± 1.37 g (high-dose group) and 1.46 ± 0.62 g (low-dose group). Of note, there were no statistical differences in the response rates when comparing patients of the 2 groups: CR was achieved in 52.6% versus 71.4% (p = 0.37) and PR in 26.3% versus 14.3% (p = 0.58) of patients in the high-dose and low-dose prednisone group, respectively (Table 4). Renal outcome was irrespective of initial prednisone doses as determined by Pearson's chi-square test of independence (p = 0.46).

Adverse events during treatment period. We recorded at least 1 infection in 21 patients (52.5%). Major infectious complications included herpes zoster in 3 patients (7.5%) and 1 pneumonia caused by *Mycoplasma pneumoniae* treated in hospital. New onset of leukopenia (≤ 3000/μl) was diagnosed in 9 patients. We observed no significant differences concerning the rate of infections in relation to the initial prednisone dose [61.4% (high-dose) and 52% (low-dose)]. Permanent amenorrhea developed in 5 (15.1%) of 33 female patients (mean age at treatment 47 ± 19.2 yrs, range 19–66 yrs).

Longterm followup. All patients were evaluated regularly after completing the treatment protocol. Treatment following IV CYC consisted of hydroxychloroquine (HCQ) alone

Table 2. Change of measures in all 40 patients during followup. Results are mean ± SD.

Measure	Baseline	After 24 mo	p
24-h urinary protein, mg	3321 ± 2531	513 ± 510	< 0.0001
Serum creatinine, mg/dl	0.9 ± 0.3	0.9 ± 0.4	0.10
C3, mg/dl	56.2 ± 20.8	87 ± 22	< 0.0001
Anti-dsDNA, IU/ml	243 ± 260	86 ± 164	< 0.0001
Hemoglobin, mg/dl	10.9 ± 1.6	12.7 ± 1.6	< 0.0001
SLAM	9.6 ± 3.6	3 ± 2	< 0.0001

SLAM: Systemic Lupus Activity Measure.

Table 3. Differences at baseline between patients with or without response after 24 months. Results are mean ± SD or n (%).

Characteristic	CR	PR	Treatment Failure	p, CR vs PR	p, CR vs NR	p, PR vs NR
No. patients	25	8	7			
Female	20 (80)	7 (87.5)	6 (85.7)	1.00	1.00	1.00
Age, yrs	29.0 ± 10.0	31.1 ± 11.1	30.6 ± 6.4	0.65	0.64	0.91
Duration of SLE, yrs	3.40 ± 2.69	4.06 ± 3.26	3.44 ± 3.17	0.62	0.98	0.72
SLAM	9.64 ± 3.45	9.00 ± 2.93	10.57 ± 5.32	0.62	0.67	0.50
Systolic blood pressure	122 ± 11	127 ± 12	128 ± 10	1.00	1.00	1.00
Serum creatinine, mg/dl	0.96 ± 0.34	0.98 ± 0.26	1.06 ± 0.31	0.87	0.47	0.58
24-h urinary protein, mg	2819 ± 2369	4505 ± 2509	3763 ± 2950	0.12	0.46	0.61
24-h urinary protein, ≥ 2.5 g	10 (40%)	7 (87.5%)	3 (42.9%)	0.053	1.00	0.20
Hemoglobin, mg/dl	10.9 ± 1.6	11.0 ± 1.8	11.0 ± 1.8	0.87	0.96	0.93
C3, mg/dl	53.5 ± 21.5	63.4 ± 19.8	58 ± 20.5	0.25	0.62	0.62
C3 ≤ 60 mg/dl	16 (64%)	2 (25%)	2 (28.5%)	0.13	0.21	1.00
Anti-dsDNA, IU/ml	251 ± 265	176 ± 255	288 ± 275	0.51	0.78	0.47
WHO class nephritis, no. patients						
Class III	14	2	1			
Class IV	10	5	4	0.26	0.13	1.00
Class V	0	1	1	0.48	0.71	1.00
				0.54	1.00	1.00
Hydroxychloroquine	8 (32)	3 (37.5)	4 (57.1)	1	0.44	0.81
Mean prednisone dosage						
at baseline, mg/day	23.8 ± 26.4	25.0 ± 21.2	23.2 ± 19.6	0.9	0.95	0.87
Prednisone dose ≥ 20 mg/day						
at baseline	10 (40)	5 (62.5)	4 (57.1)	0.48	0.71	0.24

CR: complete response; PR: partial response; NR: no response; SLAM: Systemic Lupus Activity Measure; WHO: World Health Organization; SLE: systemic lupus erythematosus.

Table 4. Differences between patients treated with prednisone < and ≥ 20 mg/day at baseline. Results are mean ± SD or n (%).

Characteristic	Prednisone < 20 mg/day, n = 21	Prednisone ≥ 20 mg/day, n = 19	p
Female	16 (76.1)	17 (89.4)	0.68
Age, yrs	31.9 ± 12.0	27.3 ± 7.1	0.15
Duration of SLE, yrs	3.81 ± 2.50	3.24 ± 3.19	0.53
Prednisone dose, mg/day, mean ± SD	9.40 (0–15)	40.0 (20–100)	< 0.001
Median	10	30	
Hydroxychloroquine treatment	10 (47.6)	5 (26.3)	0.29
SLAM	8.52 ± 2.56	10.95 ± 4.31	0.04
SLICC	0.2 ± 0.5	0.3 ± 0.5	0.25
Systolic blood pressure > 140 mm Hg	1 (4.8)	6 (28.5)	0.07
Diastolic blood pressure > 90 mm Hg	3 (14.3)	5 (26.3)	0.58
Serum creatinine, mg/dl	0.90 ± 0.16	1.07 ± 0.41	0.09
Hemoglobin, mg/dl	11.5 ± 1.1	10.3 ± 1.9	0.03
C3, mg/dl (90–180)	63.0 ± 14.3	48.7 ± 24.7	0.03
Anti-dsDNA, IU/ml (< 80)	281 ± 256	205 ± 264	0.37
24-hour urinary protein, mg	3088 ± 2445	3579.3 ± 2665	0.55
WHO class nephritis, n = 38	No biopsy: 2	No biopsy: 0	0.07
Class III	12 (63.1)	5 (26.3)	
Class IV	6 (31.5)	13 (68.4)	
Class V	1 (5.26)	1 (5.26)	
Arthritis	13 (61.9)	18 (94.7)	0.03
Rash	14 (66.7)	10 (52.6)	0.56
Serositis	6 (28.6)	13 (68.4)	0.03
Neurologic involvement	3 (14.3)	3 (15.8)	1.00
Hemolytic anemia	3 (14.3)	3 (15.8)	1.00
Thrombopenia	1 (4.7)	2 (10.5)	1.00
Leukopenia	6 (28.6)	8 (42.1)	0.45

SLAM: Systemic Lupus Activity Measure; SLICC: Systemic Lupus International Collaborating Clinics Damage Index; WHO: World Health Organization; SLE: systemic lupus erythematosus.

(18 patients), HCQ and mycophenolate mofetil (MMF; 13 patients), MMF alone (4 patients), and no specific SLE treatment besides low-dose prednisone (5 patients). Two patients died, 5 and 13 months, respectively, after the last IV CYC treatment. The cause of death in the first case was an anesthetic complication during termination of an unplanned pregnancy at age 26 years with otherwise stable SLE. In the second case, the cause of death was attributed to sepsis and treatment-resistant multisystem flare in a 21-year-old patient who had stopped all her medications prior to this event. One patient was lost to followup. The remaining 37 patients were followed for a mean of 10.4 ± 3.1 years. Fourteen (37.8%) of these 37 patients experienced a renal flare, 11 of them (78.5%) during the first 5 years after treatment. We could detect no significant differences concerning the flare rate in respect to longterm treatment.

Six of the 25 patients with CR (24%) after IV CYC experienced a flare, compared to 4 of the 8 patients (50%) with PR and 4 of the 7 patients (57.1%) with no response. Dependence between response category and occurrence of renal flares was not significant (p = 0.16; Figure 1). The Kaplan-Meier curves shown in Figure 2 indicate that the cumulative probability of an absence of flare did not differ between patients in respect to the initial prednisone regimen. All patients who experienced a flare received additional immunosuppressive therapy (MMF, n = 12, or retreatment with IV CYC, n = 2). At the last investigation, 2 patients had developed ESRD and 5 patients developed doubling of serum creatinine. The mean serum creatinine of 35 patients who did not develop ESRD did not differ significantly regarding the initial prednisone treatment (1.06 ± 0.73 mg/dl in the low-dose and 1.45 ± 1.42 mg/dl in the high-dose group; p = 0.92).

Almost all patients (92%) were still treated with low-dose prednisone (mean 4.6 mg/day). The mean prednisone dose in these patients at baseline was 23 ± 22 mg/day. In addition, 67.5% were receiving HCQ, 32.4% MMF, and 5.4% azathioprine. No avascular necrosis was noted during longterm followup. One patient developed osteoporotic fractures. Two patients experienced symptomatic coronary artery disease (myocardial infarction). One patient with a long history of smoking developed lung cancer. Five female patients experienced 6 normal pregnancies.

DISCUSSION

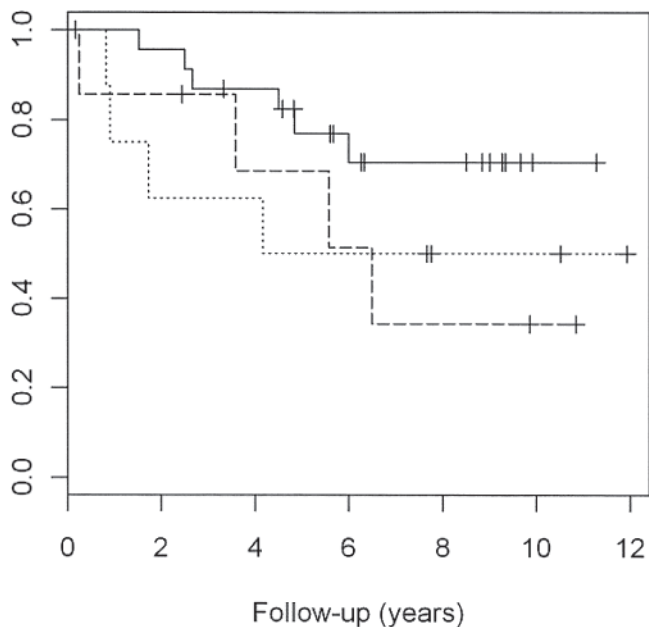In our prospective observational study, we report the out-

Figure 1. Kaplan-Meier analysis of the probability of flare during longterm followup in patients achieving complete response (solid line), partial response (dotted line), or nonresponse (dashed line) after treatment. The HR for renal flare in the complete-response group compared with the non-response group was 0.39 (95% CI 0.11–1.4, p = 0.15) and 0.87 (95% CI 0.22–3.5, p = 0.85) compared with the partial response group.
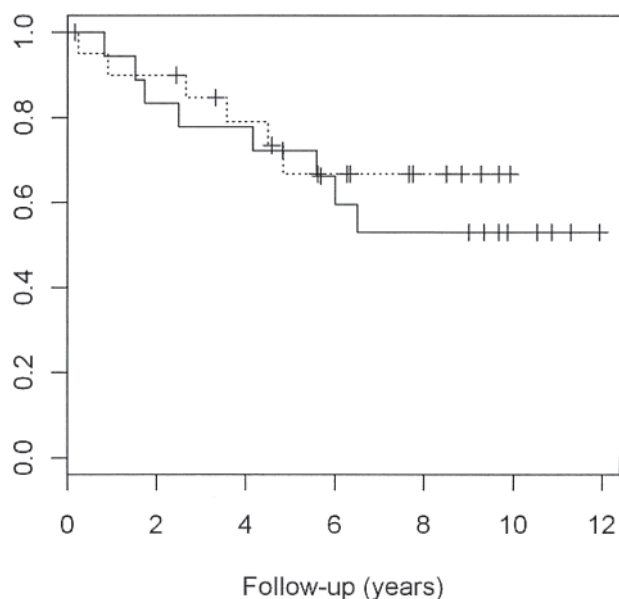

Figure 2. Kaplan-Meier analysis of the probability of an absence of flare during longterm followup in patients treated with ≥ 20 mg prednisone (solid line) versus patients treated with < 20 mg prednisone at baseline (dotted line). The HR for renal flare in the low-prednisone group compared with the high-prednisone group was 0.73 (95% CI 0.25–2.12, p = 0.57).

come of 40 white patients with a first episode of LN treated with an induction regimen consisting of IV CYC without additional methylprednisolone pulses or high doses of oral

GC commonly used for induction of remission. After 24 months, 25 patients (62.5%) met the criteria for CR and 8 patients (20%) for PR. Our study was neither designed nor powered to answer questions concerning specific predictors for complete or partial remission. While cross-study comparisons must be regarded with caution, the rates of response we observed were comparable with outcomes reported from studies using a combination of IV CYC with moderate to high doses of GC. In the NIH study, for example, renal remission at 5 years was obtained in 85% of patients in the methylprednisolone plus IV CYC combination group[8]. The Euro-Lupus Nephritis trial reported renal remission in 71% (methylprednisolone plus low-dose IV CYC group) and 54% (methylprednisolone plus high-dose IV CYC group) after a median of 41 months[9]. Definitions for CR and PR were similar in the 2 trials.

We report a mean followup of 10 years in 37 of 40 patients. It is well established that longterm followup is needed before conclusions can be drawn regarding efficacy of any immunosuppressive regimen over another in avoiding ESRD in LN[5]. At the time of the last examination, 81% of our patients had normal serum creatinine. Rates of ESRD were low in our cohort (5.4%) and were in accord with studies investigating extended followup of > 10 years in patients with similar ethnic and disease background (5%–9% in the Euro-Lupus Nephritis trial)[23]. One explanation for this might be that 95% of our patients had proteinuria below 0.5 g/day at the end of the treatment protocol. Patients in whom control of proteinuria is achieved have much better renal survival rates at 5 and 10 years (94% for both in our study) than patients who fail to achieve remission (46% at 5 years, 31% at 10 years)[24]. Fourteen (37.8%) out of 37 patients experienced a renal flare, mostly during the first 5 years after treatment. This corresponds to flare rates of 28%–45% described in the literature, depending on duration of followup[10,25,26,27,28,29]. Again, we were not able to detect differences concerning the probability of flares in the 2 prednisone groups.

There are, however, some specific characteristics of our study population that influence the generalized applicability of our results. Clinical risk factors for disease progression, evident at the time of initial presentation, included elevated serum creatinine at the time of renal biopsy, hypertension, nephrotic range proteinuria, and black and Hispanic race and ethnicity[10,28,29]. Although 38 of our patients had biopsy-proven proliferative LN, only 6 (15%) presented with renal impairment and 20 (50%) with proteinuria ≥ 2.5 g/day compared with 64% and 62%, respectively, in the NIH study[7]. Second, the duration of nephritis before treatment was 6 months at the longest and we treated the first episode of LN in each patient. The mean duration of nephritis was 24 ± 6.9 months in the NIH study and 26% of patients enrolled in the Euro-Lupus Nephritis trial had a prehistory of renal disease[8,9]. The likelihood of a successful initial out-

come is greater if therapy for LN is initiated relatively early in the course of the disease regardless of the histological subclass[10,18]. This issue was addressed in a study of 91 patients with LN who were followed for a median of 6 years. There was a much higher rate of ESRD among patients who had clinically recognized renal disease for ≥ 6 months prior to biopsy (47 vs 14 per 1000 patient-yrs in patients who had an earlier biopsy)[18]. Third, all patients in our study were white in contrast to the higher percentage of African Americans (20%−50%) randomized into the NIH studies or in recent randomized trials[7,8,30]. African American patients with LN tend to have a worse prognosis compared with white patients[17,31,32].

It should be emphasized, however, that the patients treated in our study mirror those of the patient population currently treated in our lupus clinic. Our survival rate (95% at 10 yrs) is well in line with that seen in a large series of 1000 European patients with lupus who were followed in a prospective observational study (88% survival at 10 yrs in the nephritis subgroup)[33]. Currently, milder cases of proliferative LN, for which less aggressive treatment is certainly justified, are frequently diagnosed because of prompt assessment of kidney involvement, particularly in patients with lupus in whom proteinuria or active urinary sediment without proteinuria is detected and investigated very early during regular followup visits.

Recently, an open study compared 2 different GC doses for induction treatment in LN[34]. Patients with active proliferative LN received mycophenolate sodium and were randomized to standard-dose or reduced-dose GC. The reduced initial GC dose was half that of the standard-dose group (i.e., prednisone 25 mg/day or 50 mg/day). In the study, 64.2% of 81 patients were white and the mean time since biopsy was 2.2 ± 3.1 months. Remarkably, there was no significant difference concerning response rates between the 2 study groups. The mean cumulative dose of prednisone equivalent to Week 24 was 7.1 ± 1.2 g in the standard-dose group and 4.6 ± 1.0 g in the reduced-dose group. Interestingly, in our study, the mean cumulative dose of prednisone equivalent at the same timepoint was 3.23 ± 1.37 g in our high-dose group.

We observed low rates of major infections (10%). Within the NIH study, severe infections like herpes zoster occurred in 21% of the combination therapy group[8]. Within the Euro-Lupus Nephritis trial, infections requiring inpatient antimicrobial therapy were noted in 16.6%[9]. During longterm followup, none of our patients developed avascular necrosis, which, for example, was common in the NIH study and was most prevalent in the groups that received methylprednisolone (18% and 22%, respectively, vs 11% IV CYC alone)[8].

Our study had an open-label design, which risks the introduction of bias. However, this may have been diminished because (1) all patients received the same CYC dosing regimen; (2) the prednisone dose was given irrespective of renal function and was guided by extrarenal manifestations; and (3) allocation to the high- or low-dose prednisone group was undertaken post hoc. Nevertheless, the results cannot be uncritically applied to all patients with lupus, in particular to patients with severe extrarenal disease or patients treated with either the Euro-Lupus cyclophosphamide regimen or with MMF.

On the other hand, our approach with prednisone dosing according to extrarenal manifestations takes into account that individual treatment decisions frequently have to be made in clinical practice. Thus, although caution should be exercised in extrapolating our results to other LN populations, our findings suggest that GC dosing could be reduced in the presence of concomitant use of immunosuppressive treatments like IV CYC without loss of efficacy for the management of LN. Our preliminary findings therefore clearly warrant a controlled study comparing different GC dosing regimens in patients with LN.

ACKNOWLEDGMENT

REFERENCES

1. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: Clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine 1993;72:113-24.
2. Bono L, Cameron JS, Hicks JA. The very long-term prognosis and complications of lupus nephritis and its treatment. QJM 1999;92:211-8.
3. MacGowan JR, Ellis S, Griffiths M, Isenberg D. Retrospective analysis of outcome in a cohort of patients with lupus nephritis treated between 1977 and 1999. Rheumatology 2002;41:981-7.
4. Adler M, Chambers S, Edwards C, Neild G, Isenberg D. An assessment of renal failure in an SLE cohort with special reference to ethnicity, over a 25-year period. Rheumatology 2006;45:1144–7.
5. Austin HA, Klippel JH, Balow JE. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614-69.
6. Steinberg AD, Steinberg SC. Long-term preservation of renal functioning patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisolone alone. Arthritis Rheum 1991;34:945-50.
7. Boumpas DT, Austin HA 3rd, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992; 340:741-5.
8. Gourley MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. Ann Intern Med 1996;125:549-57.
9. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido E, Ede R, et al. Immunosuppressive therapy in lupus nephritis. The Euro-lupus Nephritis Trial, a randomized trial of low-dose versus high-dose cyclophosphamide. Arthritis Rheum 2002;46:2121-31.
10. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, et

al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:971–80.

11. Gladman DD, Urowitz MB, Rahman P, Ibañez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. J Rheumatol 2003;30:1955–9.

12. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthritis Rheum 2000;43:1801-8.

13. Bruce IN, Urowitz MB, Gladman DD, Hallet DC. Natural history of hypercholesterolemia in systemic lupus erythematosus. J Rheumatol 1999;26:2137-43.

14. Petri M. Detection of coronary artery disease and the role of traditional risk factors in the Hopkins Lupus Cohort. Lupus 2000;9:170-5.

15. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008;67:195–205.

16. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2007;66:1560–7.

17. Contreras G, Pardo V, Cely C, Borja E, Hurtado A, De La Cuesta C, et al. Factors associated with poor outcomes in patients with lupus nephritis. Lupus 2005;14:890-5.

18. Faurschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: Diagnostic and therapeutic delay increases the risk of terminal renal failure. J Rheumatol 2006;33:1563-9.

19. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

20. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.

21. Liang MH, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 1989;32:1107-18.

22. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9.

23. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: Results from the MAINTAIN Nephritis Trial. Ann Rheum Dis 2010;69:2083-9.

24. Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. Am J Kidney Dis 2000;35:904-14.

25. Houssiau FA, Ginzler EM. Current treatment of lupus nephritis. Lupus 2008;17:426-30.

26. Moroni G, Banfi G, Ponticelli C. Clinical status of patients after 10 years of lupus nephritis. Q J Med 1992;84:681-9.

27. Illei GG, Takada K, Parkin D, Austin HA, Crane M, Yarboro CH, et al. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: Long-term followup of a cohort of 145 patients participating in randomized controlled studies. Arthritis Rheum 2002;46:995-1002.

28. Appel GB, Cohen DJ, Pirani CL, Meltzer JI, Estes D. Long-term follow-up of patients with lupus nephritis. A study based on the classification of the World Health Organization. Am J Med 1987;83:877–85.

29. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: Contributions of clinical and histologic data. Kidney Int 1994;45:544–50.

30. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103-12.

31. Mok CC. Prognostic factors in lupus nephritis. Lupus 2005; 14:39-44.

32. Dooley MA, Hogan S, Jennette C, Falk R. Glomerular Disease Collaborative Network. Cyclophosphamide therapy for lupus nephritis: Poor renal survival in black Americans. Kidney Int 1997;51:1188-95.

33. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: A comparison of early and late manifestations in a cohort of 1,000 patients. Medicine 2003;82:299–308.

34. Zeher M, Doria A, Lan J, Aroca G, Jayne D, Boletis I, et al. Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis. Lupus 2011;20:1484-93.