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Early Response to Immunosuppressive Therapy Predicts Good Renal Outcome in Lupus Nephritis

Lessons From Long-Term Followup of Patients in the Euro-Lupus Nephritis Trial

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Objective. **In the Euro-Lupus Nephritis Trial (ELNT), 90 patients with lupus nephritis were randomly assigned to a high-dose intravenous cyclophosphamide (IV CYC) regimen (6 monthly pulses and 2 quarterly pulses with escalating doses) or a low-dose IV CYC regimen (6 pulses of 500 mg given at intervals of 2 weeks), each of which was followed by azathioprine (AZA). After a median followup of 41 months, a difference in efficacy between the 2 regimens was not observed. The present analysis was undertaken to extend the followup and to identify prognostic factors.**

Methods. **Renal function was prospectively assessed quarterly in all 90 patients except 5 who were lost to followup. Survival curves were derived using the Kaplan-Meier method.**

Results. **After a median followup of 73 months, there was no significant difference in the cumulative probability of end-stage renal disease or doubling of the serum creatinine level in patients who received the low-dose IV CYC regimen versus those who received the high-dose regimen. At long-term followup, 18 patients (8 receiving low-dose and 10 receiving high-dose treatment) had developed permanent renal impairment and were classified as having poor long-term renal outcome. We demonstrated by multivariate analysis that early response to therapy at 6 months (defined as a decrease in serum creatinine level and proteinuria <1 gm/24 hours) was the best predictor of good long-term renal outcome.**

Conclusion. **Long-term followup of patients from the ELNT confirms that, in lupus nephritis, a remission-inducing regimen of low-dose IV CYC followed by AZA achieves clinical results comparable with those obtained with a high-dose regimen. Early response to therapy is predictive of good long-term renal outcome.**

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The pioneering studies by investigators at the National Institutes of Health (NIH) have demonstrated the importance of intravenous cyclophosphamide (IV CYC) in the management of lupus nephritis (1–4), although the optimal immunosuppressive regimen has not been clearly established. Among other issues, the dosage and the duration of CYC therapy are debated, in particular given the potential side effects of CYC.

In the Euro-Lupus Nephritis Trial (ELNT), a multicenter prospective study, we tested the hypothesis that good long-term clinical results could be achieved using lower doses of IV CYC than those prescribed in the classic NIH regimen. By minimization, we randomly assigned lupus patients with biopsy-proven proliferative glomerulonephritis to receive a low-dose IV CYC regimen (6 pulses at a fixed dose of 500 mg, given at 2-week intervals) or a high-dose IV CYC regimen (6 monthly pulses and 2 quarterly pulses with escalating doses); in both the low-dose and the high-dose regimens, the IV CYC treatment course was followed by treatment with azathioprine (AZA), used as remission-maintaining therapy. After a median followup of 41 months, there was no significant difference in efficacy between the 2 groups (5).

In the study reported herein, we extended the analysis over a longer-term followup of the patients in the 2 treatment groups in the ELNT. We identified prognostic factors for long-term renal outcome, with special emphasis on the kinetics of the initial response to immunosuppressive therapy.

PATIENTS AND METHODS

Patient selection. Between September 1996 and September 2000, 90 patients with systemic lupus erythematosus according to the American College of Rheumatology criteria (6), who were age 14 years or older and had biopsy-proven proliferative lupus glomerulonephritis (World Health Organization class III, IV, Vc, or Vd) and proteinuria (≥500 mg/24 hours), were enrolled in the ELNT at 19 centers in Europe. Inclusion and exclusion criteria have been described elsewhere (5). Of the 90 patients, 20 (22%) presented with renal impairment and 25 (28%) with nephrotic syndrome. The study was approved by the ethics committees of each participating hospital, and written informed consent was obtained from all patients.

Treatment. All patients received 3 IV pulses of 750 mg methylprednisolone (1 per day on 3 successive days), followed by oral glucocorticoid therapy at an initial dosage of 0.5 mg prednisolone equivalent /kg/day for 4 weeks. A dosage of 1 mg/kg/day was allowed in critically ill patients (renal impairment or severe extrarenal disease). After 4 weeks, glucocorticoid treatment was tapered by 2.5 mg prednisolone equivalent every 2 weeks. Low-dose glucocorticoid therapy (5–7.5 mg prednisolone/day) was maintained at least until month 30 after enrollment and could be stopped thereafter at the discretion of the treating physicians.

All patients received IV CYC therapy beginning on the day of enrollment. They were randomized into 2 groups, high-dose or low-dose IV CYC treatment, by minimization (7). Patients assigned to the high-dose group received 8 IV CYC pulses within 1 year, i.e., 6 monthly pulses followed by 2 quarterly pulses. The initial CYC dose was 0.5 gm/m^2 of body surface area, and the subsequent doses were increased by 250 mg according to the white blood cell count nadir measured on day 14 (8), with a maximum of 1,500 mg per pulse. Patients assigned to the low-dose group received 6 IV CYC pulses at a fixed dose of 500 mg, in 2-week intervals. The use of mesna was left to the decision of the physician. In both treatment groups, AZA (2 mg/kg/day) was started 2 weeks after the last CYC injection and continued until at least month 30 after enrollment. Hypertension (diastolic blood pressure ≥90 mm Hg) was treated initially with angiotensin-converting enzyme inhibitors (ACE inhibitors), unless they were contraindicated. The introduction of ACE inhibitors was not allowed as antiproteinuric therapy within the first 6 months in normotensive patients. Contraception was prescribed in all fertile, sexually active women, and they were warned about the potential deleterious effect that pregnancy could have on their disease, at least during the first 30 months after study enrollment.

End points. Renal function (based on serum creatinine level) was assessed on a regular basis (i.e., quarterly) in all 90 patients except 5 who were lost to followup. The median duration of followup was 73 months.

Paraffin-embedded kidney biopsy specimens obtained at baseline were reviewed by one of the authors (J-PC), who was blinded to the randomization and outcome data and who evaluated the specimens for activity and chronicity indices according to the method of Morel-Maroger et al (9), as described elsewhere (5). In some patients, repeat biopsies had been performed, and these specimens were similarly reviewed.

Statistical analysis. Survival curves were derived using the Kaplan-Meier method and were statistically tested by log rank test. We calculated hazard ratios and their 95% confidence intervals using the univariate Cox proportional hazards model. Patients who were withdrawn from the trial were included in Kaplan-Meier analyses (intent-to-treat analyses). Within-group *P* values were calculated by repeated-measures analysis of variance. Between-group *P* values were calculated by analysis of covariance with adjustment for baseline values. Logistic regression analysis was used for multivariate analysis of outcome predictors. Unpaired *t*-tests, Wilcoxon's signed rank tests, chi-square tests, and Fisher's exact tests were used as appropriate.

RESULTS

Long-term followup of patients in the Euro-Lupus Nephritis Trial. Of the 90 patients randomized in the ELNT, 5 were lost to followup. Serum creatinine values were obtained on a regular basis in the 85 remaining patients. After a median followup period of 73 months, renal function was permanently impaired at

last followup in 21% of the patients (20% in the low-dose group and 23% in the high-dose group), as indicated in Table 1. The Kaplan-Meier curves shown in Figure 1 indicate that there was no greater cumulative probability of ESRD (Figure 1A) or doubling of the serum creatinine value (Figure 1B) in patients receiving the low-dose IV CYC regimen than in those given the high-dose IV CYC regimen.

Three of the 85 patients for whom long-term followup data were available had died: the first died of multiorgan failure at month 1, the second died of an unrelated cause (breast cancer) at month 43, and the third died of septic shock at month 53 (7 months after having received immunoablative doses of CYC, after withdrawal from the ELNT). All 3 of these patients had been initially randomized to the low-dose CYC group. Since renal function data had been recorded shortly before their deaths, they were included in the long-term renal outcome analysis.

At 5 of the study centers, the local ethics committee approved performance of repeat kidney biopsies. Thus, a second renal biopsy specimen was obtained from 20 patients (11 in the low-dose group and 9 in the high-dose group), after a mean ± SD followup time of 27 ± 7 months. The mean ± SD activity index score declined significantly between the baseline and the followup biopsies, in both the low-dose group (from 13.0 ± 5.3 to 4.6 ± 6.1; $P = 0.005$ by Wilcoxon's signed rank test) and the high-dose group (from 10.3 ± 7.4 to 2.4 ± 1.1; $P = 0.011$). In contrast, the chronicity index score did not increase significantly between the baseline and followup biopsies in either the low-dose group (from 0.8 ± 1.0 to 1.1 ± 1.1) or the high-dose group (from 0.7 ± 0.7 to 0.6 ± 0.9).

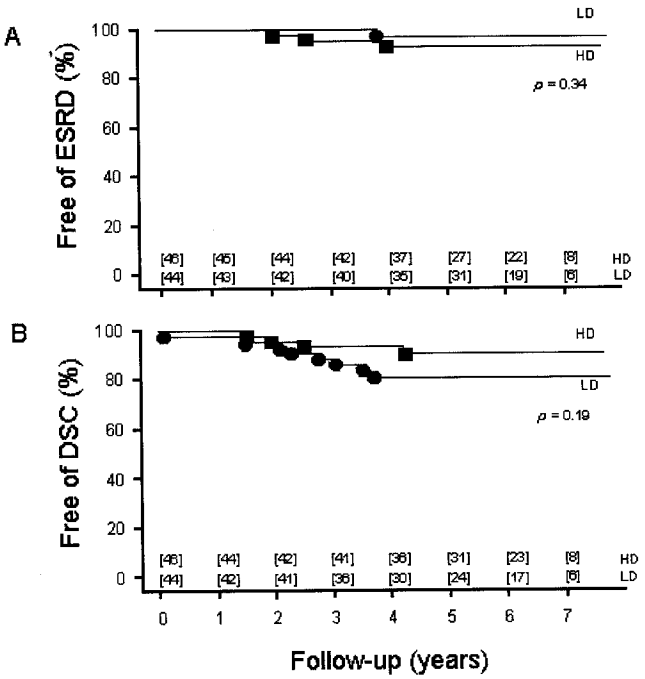

Figure 1. Kaplan-Meier curves of the probability of absence of end-stage renal disease (ESRD) (**A**) or of doubling of the serum creatinine value (DSC) (**B**). Patients were randomized to receive a low-dose (LD) regimen (circles) or a high-dose (HD) regimen (squares) of intravenous cyclophosphamide, followed by azathioprine. Survival curves were tested statistically by log rank test. In the low-dose group, the hazard ratio was 0.35 (95% confidence interval 0.04–3.37) for ESRD and 2.2 (95% confidence interval 0.66–7.27) for DSC. Numbers along the abscissa are the number of patients at risk at each time point. Analysis was by intent-to-treat.

Table 1. Renal function at last followup, by treatment group*

Renal function	All patients (n = 85)	High-dose IV CYC group (n = 44)	Low-dose IV CYC group (n = 41)
Normal	67	34	33
Permanently impaired	18	10	8
End-stage renal disease	4	3	1
Doubling of serum creatinine	8	1	7
Impaired renal function without doubling of serum creatinine	6	6	0

* Permanently impaired renal function was defined as a serum creatinine value that was repeatedly ≥1.4 mg/dl. IV CYC = intravenous cyclophosphamide.

Prognostic factors. Patients were classified as having good (n = 67) or poor (n = 18) long-term renal outcome based on normal or repeatedly impaired serum creatinine values at last followup. As indicated in Table 2, baseline clinical, biologic, and pathologic data did not differ between good and poor long-term renal responders, except for the higher serum creatinine values in patients with a poor outcome.

We next analyzed whether the kinetics of the response within the first 6 months of therapy differed between the 2 long-term renal outcome groups. Interestingly, as indicated in Table 3, serum creatinine levels, serum albumin levels, and proteinuria had improved significantly more during the first 6 months of therapy in the group with good long-term renal outcome. In contrast, scores on the European Consensus Lupus Activity Measure (10) and serum C3 titers had improved simi-

Table 2. Baseline data in the 2 renal outcome groups*

	Good long-term renal outcome group	Poor long-term renal outcome group	*P*
Serum creatinine, mg/dl	1.09 ± 0.54	1.47 ± 0.97	0.03
Serum albumin, gm/dl	3.08 ± 0.60	2.94 ± 0.56	0.36
24-hour urinary protein, gm	3.03 ± 2.49	3.23 ± 2.25	0.76
Serum C3, mg/dl	56 ± 25	54 ± 21	0.80
ECLAM score	6.95 ± 2.08	6.06 ± 1.55	0.09
Systolic BP, mm Hg	134 ± 22	136 ± 20	0.83
Diastolic BP, mm Hg	83 ± 16	84 ± 17	0.88
Activity index score	9.6 ± 6.2	11.5 ± 5.7	0.24
Chronicity index score	0.8 ± 0.9	0.9 ± 0.7	0.47
WHO class III/IV/V, no.	13/46/5	4/11/3	0.50

* Between-group *P* values were calculated by chi-square test for World Health Organization (WHO) class and by unpaired *t*-test for other parameters. Activity and chronicity index scores were calculated as described in refs. 5 and 9. Except where indicated otherwise, values are the mean ± SD. ECLAM = European Consensus Lupus Activity Measurement; BP = blood pressure.

larly in the 2 groups. The between-group differences for serum albumin and 24-hour urinary protein levels remained statistically significant when corrected (by analysis of covariance) for baseline serum creatinine values ($P = 0.017$ and $P < 0.0001$ for serum albumin at 3 months and 6 months, respectively; $P = 0.018$ and $P = 0.011$ for 24-hour urinary protein at 3 months and 6 months, respectively).

The percentage of patients whose 24-hour urinary protein value was reduced by at least 50% or by at least 75% at 6 months was significantly higher in the good long-term renal outcome group than in the poor

Table 3. Kinetics of response in the good and poor long-term renal outcome groups*

Parameter, time	Good long-term renal outcome group, mean ± SD	Poor long-term renal outcome group, mean ± SD	Between-group *P*
Serum creatinine, mg/dl			
Baseline	1.09 ± 0.54	1.47 ± 0.97	
Month 3	0.92 ± 0.22	1.11 ± 0.27	0.028
Month 6	0.89 ± 0.24	1.12 ± 0.22	0.005
Within-group *P*	0.0009	0.161	
Serum albumin, gm/dl			
Baseline	3.08 ± 0.60	2.94 ± 0.56	
Month 3	3.79 ± 0.51	3.44 ± 0.55	0.009
Month 6	3.99 ± 0.48	3.42 ± 0.47	0.000
Within-group *P*	<0.0001	0.0005	
24-hour urinary protein, gm			
Baseline	3.03 ± 2.49	3.23 ± 2.25	
Month 3	1.48 ± 1.28	3.59 ± 3.79	0.115
Month 6	1.15 ± 1.41	2.55 ± 2.67	0.026
Within-group *P*	<0.0001	0.154	
ECLAM score			
Baseline	6.95 ± 2.08	6.06 ± 1.55	
Month 3	2.39 ± 1.75	2.29 ± 1.40	0.974
Month 6	1.84 ± 1.57	2.18 ± 1.33	0.262
Within-group *P*	<0.0001	<0.0001	
Serum C3, mg/dl			
Baseline	56 ± 25	54 ± 21	
Month 3	86 ± 26	80 ± 19	0.378
Month 6	86 ± 22	79 ± 27	0.313
Within-group *P*	<0.0001	0.0002	

* Within-group *P* values were calculated by repeated-measures analysis of variance. Between-group *P* values were calculated by analysis of covariance, after adjustment for the baseline value of the tested parameter. ECLAM = European Consensus Lupus Activity Measurement.

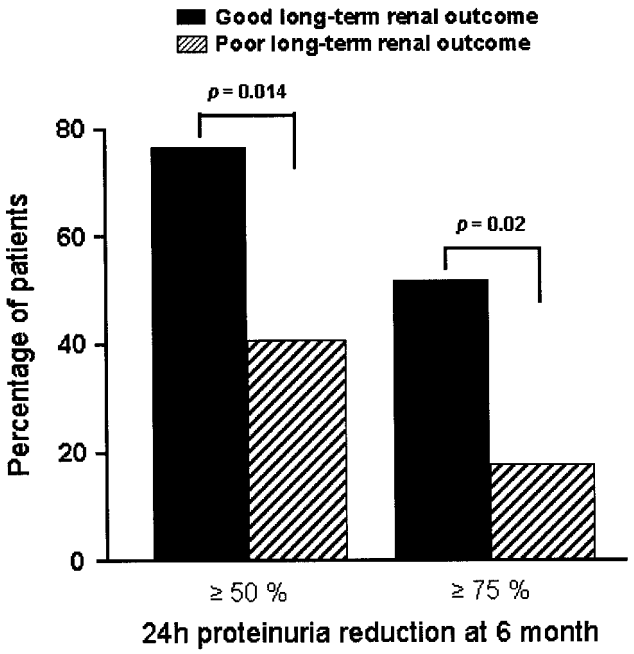

Figure 2. Percentage of patients in the good long-term renal outcome group and the poor long-term renal outcome group who had at least a 50% reduction or at least a 75% reduction in 24-hour urinary protein levels at 6 months. *P* values were calculated by Fisher's exact test.

long-term renal outcome group (Figure 2). The positive predictive value of a 75% decrease in proteinuria at 6 months for good long-term renal outcome was 90%. Similar results were obtained when absolute levels of improvement were analyzed: the positive predictive value of a 24-hour urinary protein level <1 gm at 6 months for good long-term renal outcome was 87%. Importantly, the use of ACE inhibitors within the first 6 months of therapy did not differ between patients who did and those who did not experience a 75% decrease in proteinuria at 6 months (31% and 38%, respectively), thereby reducing the risk of bias linked to early ACE inhibitor use.

To complete the study of predictors of long-term renal outcome, we performed a multivariate analysis using a logistic regression model. As indicated in Table 4, of the 13 covariates tested, only a decrease in the serum creatinine value at 6 months and a 24-hour urinary protein level of <1 gm at 6 months were predictors of good long-term renal outcome. Interestingly, none of the baseline parameters had such a predictive value. A subset analysis performed on patients with baseline renal impairment (serum creatinine ≥1.4 mg/dl) for whom kinetics data and long-term renal outcome were known indicated a similar trend, namely, that early response to therapy had prognostic value (Table 5).

DISCUSSION

The prospective data presented here confirm that good long-term results in patients with proliferative lupus glomerulonephritis can be achieved by remission-inducing therapy with a low-dose IV CYC regimen (cumulative dose 3 gm) followed by AZA as remission-maintaining treatment. Of note, only 1 patient of the 44 randomized to receive this regimen (now referred to as the Euro-Lupus regimen) had developed ESRD after a followup of 6 years. Whether these results can be extrapolated at 10 years is obviously speculative. How-

Table 4. Multivariate analysis of predictors of good long-term renal outcome*

Variable	*P*	Odds ratio	95% confidence interval
Age (<30 years)	0.99	1.0	0.2–5.1
Sex (female)	0.98	0	NA
Baseline diastolic pressure (<90 mm Hg)	0.77	1.3	0.3–5.9
Baseline serum creatinine (<1.4 mg/dl)	0.06	7.7	0.9–65.6
Baseline serum albumin (3 gm/dl)	0.31	0.4	0.1–2.2
Baseline 24-hour urinary protein (<3 gm)	0.81	0.8	0.1–4.6
WHO class (III or Vc)	0.32	0.3	0–3.4
Activity index (<10)	0.53	2.0	0.2–18.4
Chronicity index (<1)	0.11	4.0	0.7–21.9
Treatment allocation (high-dose IV CYC)	0.33	0.4	0.1–2.3
ACE inhibitor use (yes)	0.34	2.3	0.4–12.5
Serum creatinine at 6 months (decreased)	0.01	14.9	2.0–111.8
24-hour urinary protein at 6 months (<1 gm)	0.03	6.3	1.2–34.4

* The analysis was performed using a logistic regression model. NA = not applicable; WHO = World-Health Organization; IV CYC = intravenous cyclophosphamide; ACE inhibitor = angiotensin-converting enzyme inhibitor.

Table 5. Kinetics of response: subset analysis restricted to patients presenting with renal impairment at baseline*

Parameter, time	Good long-term renal outcome group, mean ± SD	Poor long-term renal outcome group, mean ± SD	Between-group *P*
Serum creatinine, mg/dl			
Baseline	2.05 ± 0.70	2.42 ± 1.22	
Month 3	1.07 ± 0.30	1.37 ± 0.29	0.141
Month 6	1.04 ± 0.27	1.28 ± 0.33	0.186
Within-group *P*	0.0002	0.089	
Serum albumin, gm/dl			
Baseline	2.88 ± 0.43	2.74 ± 0.46	
Month 3	3.79 ± 0.44	3.33 ± 0.75	0.040
Month 6	4.03 ± 0.59	3.32 ± 0.43	0.046
Within-group *P*	0.0001	0.208	
24-hour urinary protein, gm			
Baseline	2.61 ± 1.50	4.92 ± 2.49	
Month 3	1.58 ± 1.52	5.93 ± 5.11	0.092
Month 6	1.18 ± 1.96	4.04 ± 2.89	0.122
Within-group *P*	0.099	0.407	

* Within-group *P* values were calculated by repeated-measures analysis of variance. Between-group *P* values were calculated by analysis of covariance, after adjustment for the baseline value of the tested parameter.

ever, based on the number of patients in both groups who had developed impaired renal function after the long-term followup reported here (20% and 23% in the low-dose group and the high-dose group, respectively), it is unlikely that further followup will reveal a difference. In a previous report (5), we had already shown that episodes of severe infection were less than half as common in patients given a low-dose IV CYC regimen (7 episodes, versus 17 in the high-dose group), although this difference was not statistically significant. From those results taken together with the findings reported herein, we propose that the Euro-Lupus regimen is a suitable alternative to a regimen of long-term, high-dose IV CYC, at least for European patients. Our results are consistent with those described in a recent report by Contreras et al indicating that short-term therapy with IV CYC followed by maintenance therapy with AZA or mycophenolate mofetil (MMF) is safer—and even more efficacious—than long-term therapy with IV CYC (11), although some caveats can be raised (12).

The present analysis was also aimed at identifying prognostic factors in lupus glomerulonephritis. Many reports (13–17) have already described factors that are associated with poor prognosis, including young age at onset of nephritis, African American ethnicity, hypertension and renal impairment at baseline, and poor pathologic findings on kidney biopsy, such as the presence of cellular crescents in ≥50% of the glomeruli or an elevated chronicity index related to interstitial and/or glomerular fibrosis. It should be stressed, however, that most of these studies were retrospective.

Only a few studies have analyzed whether the initial response to therapy predicts long-term renal outcome. Levey et al found that treatment response, defined as resolution of an initial serum creatinine elevation within 48 weeks, was prognostic in a cohort of 63 patients with severe, glucocorticoid and oral CYC–treated lupus nephritis in the Lupus Nephritis Collaborative Study (18). Laitman and colleagues, in a study that included a relatively small number of patients (n = 39), showed that patients whose serum CH50 titers were consistently normal had better outcome than those in whom CH50 values were found to be normal only transiently or not at all (19). In the present study we have convincingly demonstrated by multivariate analysis that an early response to therapy at 6 months (decrease in the serum creatinine level and a 24-hour urinary protein level <1 gm) is the best predictor of good long-term renal outcome, compared with all baseline parameters tested as other covariates. These prospectively obtained data confirm the findings obtained by Fraenkel et al in a study using data that were accumulated retrospectively (20). Those investigators reported that change in proteinuria at 1 year was a powerful predictor of long-term outcome in a group of 85 patients who had received various immunosuppressive regimens.

Whether the length and intensity of immunosuppression should be tailored according to the initial

response to therapy becomes a key issue not addressed in the ELNT. Our results would suggest that a more incisive strategy should be adopted for patients whose proteinuria does not dramatically improve after 3 or 6 months of IV CYC therapy. In such patients, MMF might be an option as rescue therapy. This immunosuppressive drug has become widely used in lupus nephritis since the pioneering work of Chan et al, who demonstrated its potential as remission-inducing therapy in a short-term clinical trial in which it was compared with oral CYC (21). In a recent trial (22), MMF was shown to be superior to IV CYC as remission-inducing therapy, although it should be stressed that only very short-term responses have been evaluated to date.

Taken together, the data presented here confirm that the Euro-Lupus regimen might offer an alternative to the classic NIH regimen for the treatment of lupus glomerulonephritis. Moreover, our results illustrate the critical importance of early response to immunosuppressive therapy.

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