Editorial

Early Diagnosis and Treatment in Lupus Nephritis: How We Can Influence the Risk for Terminal Renal Failure

The determination of prognostic factors in rheumatic diseases has 2 different important goals: Primarily, it helps clinicians identify patients with high risk for organ damage who need a more aggressive treatment schedule. Second, it helps identify prognostic factors that might be modifiable, thereby leading to decisions that result in a better outcome for patients.

Nephritis is a frequent manifestation of systemic lupus erythematosus (SLE) that has a strong impact on overall prognosis of the disease, due to the risk of terminal renal failure[1]. Presently the rate of endstage renal disease (ESRD) in lupus nephritis (LN) is about 5—10%[2,3], which is considerably less in comparison to earlier decades[1,3]. Moreover, overall mortality has improved[4].

The reason for this improvement in prognosis of LN seems to be multifactorial. The introduction of immunosuppressive drugs in addition to corticosteroids as a standard treatment of diffuse proliferative glomerulonephritis (GN) has significantly improved outcome[5,6]. Further, although only limited data are available[7], adjunct treatments such as angiotensin-converting enzyme (ACE) inhibitors might also be a critical factor. In a recent report we compared the outcome of LN diagnosed in the 1980s and the 1990s[3]. We showed that early initiation of immunosuppressive treatment might be critical for the outcome of patients with LN. While 40% of the patients diagnosed with LN during the 1980s finally developed ESRD after a mean followup of 94 months, no patient at our center with LN diagnosed in the 1990s had this outcome during a mean followup of 24 months. Although this observation period was still short, Kaplan-Meier analysis showed a significantly better outcome in the 1990s in comparison to the previous decade. While treatment schedules including use of corticosteroids, immunosuppressive drugs, or ACE inhibitors were not significantly different in the groups in each decade, the time from first appearance of proteinuria until biopsy was 15.4 months in the 1980s and only 3.9 months in the 1990s at our center, most likely explaining the different outcomes between the 2 decades[3].

The importance of early biopsy and start of treatment as a prognostic factor for LN has been shown by other groups. Esdaile, *et al*[8,9] showed that a prolonged duration of renal disease prior to the first renal biopsy was associated with a higher frequency of renal insufficiency in patients with LN[9]. Further, they demonstrated that this was not due to a selection bias, but truly reflected the beneficial effect of early treatment on the prognosis of LN.

In this issue of *The Journal*, Faurschou, *et al*[10] strongly support our observation concerning early intervention in LN, and underline its importance as a modifiable prognostic factor in LN. The authors analyze the outcome of 91 patients with biopsy-proven LN over a median followup time of 6.1 years (0.1—30). This cohort consisted of 61% with diffuse proliferative GN (World Health Organization IV), 18% mesangial GN (WHO II), 11% focal proliferative GN (WHO III), and 10% membranous GN (WHO V). Two patients with advanced sclerosing GN (WHO VI) were excluded from the investigation.

The cumulative incidence of ESRD after 1, 5, and 10 years was 3.5%, 15%, and 17%, respectively. As patients diagnosed as having LN between 1975 and 1995 were included, this frequency might be comparable to those of other centers[1,3,11]. Using multivariate regression analyses, they identified duration of nephritis symptoms > 6 months prior to biopsy as the strongest independent risk factor for ESRD, with a relative hazard ratio of 9.3. Further on they identified s-creatinine > 140 μmol/l at the time of biopsy and the histological findings of diffuse proliferative GN and tubular atrophy, with relative hazard ratios of 5.6, 8.9, and 3.1, respectively, as predictors of ESRD. These data are consistent with other publications (Table 1).

However, another important aspect of the study empha-

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Table 1. Adverse prognostic factors in LN as reported in recent studies.

Kidney Histology	Clinical/Biochemical Characteristics	Disease Course	Other
Diffuse proliferative GN[7,12]	Hypercreatinemia[11,17-19]	Low response to initial treatment[11,23]	Smoking[21]
Active glomerular and tubulointerstitial lesions[7,12,16]	Marked proteinuria[8]		African population group[17]
Chronic parenchymal injury[7,12,17]	Hypertension[20,.21]	Frequency of flares[24]	Male sex[19]
			Delay between onset of renal disease and biopsy[3,9,22]

sizes the value of early kidney biopsy in the course of suspected renal manifestation in SLE: intensive immunosuppressive treatment was not started in any of these unselected patients between the onset of nephritis symptoms and renal biopsy. This was the case although in 30 out of the 91 patients (33%) the nephritic symptoms, defined as the presence of ≥ 5 erythrocytes per high power field, had lasted longer than 6 months before biopsy. In all cases immunosuppressive therapy was instituted or intensified within one month following kidney biopsy, i.e., cyclophosphamide in 54 of 91 patients (59%). Although the value of the histological staging of LN as a prognostic factor is undisputed[2,12], some authors state that in the presence of renal dysfunction, proteinuria, an elevated s-creatinine, or hypertension, the kidney biopsy result adds only limited additional prognostic information[8,13,14]. However, the present data show that clinicians tend to wait for histological identification of severe LN before initiating potentially harmful treatment with an immunosuppressive drug. This treatment delay is critical for the prognosis of LN.

In contrast to Esdaile, *et al*, who (due to a relatively small number of patients with ESRD) used the composite endpoint of renal insufficiency and death attributable to renal failure, Faurschou, *et al* used the more stringent endpoint of ESRD only. Moreover, although Esdaile's drug of choice was azathioprine (given in 88% of the patients after biopsy), Faurschou, *et al* prescribed cyclophosphamide, thought to be the more potent immunosuppressive drug, in 59% of their patients. Finally, the value of Faurschou's study is further augmented by the large cohort of 91 patients, a homogenous population of Caucasian patients, and a long mean followup time of 6.1 years.

However, several questions remain unanswered for clinicians who care for patients with LN: Which patients should be subjected to kidney biopsy? Huong, *et al*[15] showed in a large series that 85% of patients with SLE and nephrotic syndrome at the time of kidney biopsy had either membranous or diffuse proliferative GN. In contrast, only 13% of the patients with less than 0.5 g/day proteinuria had these histological findings, which are usually thought to need intensive immunosuppressive therapy in order to prevent progression to renal insufficiency. Proteinuria less than 0.5 g/day in SLE therefore is probably associated with a reduced risk of severe forms of LN. In selected cases of LN with low protein loss a strategy of wait and watch might therefore be justified.

A second unanswered question is whether progression to diffuse proliferative GN can be prevented in patients with focal proliferative GN. This transformation from a more favorable prognosis to a high-risk histological grade of LN occurred in 6 out of 48 patients who were subjected to a repeated biopsy in the work of Huong, *et al*[15]. Treatment with azathioprine, low-dose steroids, or even only hydroxychloroquine might be able to prevent this "upgrading," which would further support the need for early kidney biopsy in suspected LN. This, as well as new treatment options in patients with refractory courses of LN, will be the subject of future clinical trials.

So far, recognition of the importance of early diagnosis and use of current treatment options in LN means major progress in the prevention of irreversible damage and ESRD in SLE. Tight control and frequent monitoring of patients with SLE and risk of renal manifestations is a potent way to improve the outcome of these patients.

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