

# DETERMINANTS OF PATIENT SURVIVAL IN SYSTEMIC LUPUS ERYTHEMATOSUS— FOCUSING ON LUPUS NEPHRITIS

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**Introduction:** Systemic lupus erythematosus is more prevalent among Asians, African Americans, and Hispanics than in Caucasians. Progress in its management over the past few decades has resulted in improved patient survival, although a considerable proportion of patients are still afflicted with long-term illnesses such as chronic renal failure secondary to lupus nephritis.

**Methods and Results:** This is a review of the factors that affect the survival of patients with systemic lupus erythematosus, including discussion of the measures that can further improve the clinical outcomes and prevent long-term complications. Recent advances in the treatment of severe lupus nephritis are emphasized, especially with regard to the minimization of treatment-related adverse events.

**Conclusions:** While the prognosis of patients with severe lupus manifestations continues to improve, prevention of relapse remains a clinical challenge. Concomitant attention to health economics and sociopolitical issues is required to ensure that all patients can benefit from scientific progress in the understanding and treatment of severe lupus erythematosus. (*Ethn Dis.* 2006;16[suppl 2]:S2-66–S2-69)

**Key Words:** Cyclophosphamide, Ethnicity, Lupus Nephritis, Mycophenolate Mofetil, Survival

## INTRODUCTION

Much progress has been made over the past 50 years in the management of systemic lupus erythematosus. The efficacy of corticosteroid treatment for severe lupus was established in the mid-1940s; diagnosis was improved with antinuclear antibody and anti-DNA antibody assays in the following decade; renal biopsy, renal replacement therapies, and cytotoxic agents became available in the 1960s and 1970s; the histologic classification of lupus nephritis has been repeatedly refined since the 1970s; and immunosuppressive treatment regimens and the prevention and treatment of complications have continued to improve over the past few decades. As a result, the prognosis of patients with severe lupus has shown continuous improvement,<sup>1</sup> and the improved outcome is related to earlier diagnosis, prompt and effective treatment, and better supportive care. 10-year patient survival rates of up to 80% were reported in patients enrolled in the 1970s and 1980s,<sup>2,3</sup> while a 10-year survival of >90% has been observed in subsequent inception cohorts.<sup>4</sup> With present treatments, lupus nephritis is not a major cause of end-stage renal failure. Nevertheless, lupus nephritis remains an important secondary cause of renal disease after diabetes mellitus and hypertension, especially among Asian populations.

## FACTORS THAT INFLUENCE OUTCOME AND SURVIVAL

The outcome of patients with lupus nephritis, with regard to patient and renal survival, is influenced by disease manifestations, patient characteristics,

and treatment received (Table 1). While the effects of some modulating factors are observed early on, the consequence of others may only be noticeable on long-term follow-up. Some of these modulating factors, such as the efficacy and/or adverse effects of treatment, are amenable to modification. Even irreversible factors, such as inherent patient characteristics or established parenchymal damage affecting involved organs, can still influence clinical decisions, and some are potentially preventable in the early stage.

## Ethnic and Geographical Variations

Ethnic variations in the severity and control of hypertension, and consequently the progression of chronic renal failure, have been observed. With regard to immunologic differences, recent data show that while African American subjects require a higher dose of mycophenolate mofetil compared with Caucasians to prevent acute renal allograft rejection, the two ethnic groups demonstrate equivalent pharmacokinetics.<sup>5</sup> Similarly, African-American patients with diffuse proliferative lupus nephritis showed worse treatment outcomes compared with their Caucasian counterparts despite similar treatment with cyclophosphamide, with five-year renal survival rates of 58% and 95%, respectively.<sup>6</sup> These observations could imply true biological differences, ie, that patients of African origin with immune-mediated kidney diseases may have inherently more active but inappropriate immune responses as well as an increased rate of fibrotic damage compared to Caucasians. However, the observed clinical differences are likely due, at least in part, to variations in compliance, access to medical care, and socioeconomic

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**Table 1. Factors that influence the outcome and survival of patients with systemic lupus erythematosus**

Disease related	<ul style="list-style-type: none"> <li>• neurologic and pulmonary manifestations associated with less favorable prognosis</li> <li>• renal involvement associated with poor clinical outcome including reduced patient survival rates, although the relative risk has been decreasing over the past few decades</li> <li>• less favorable outcomes associated with vascular manifestations, severe irreversible organ damage, repeated major relapses, and the antiphospholipid syndrome</li> </ul>
Treatment related	<ul style="list-style-type: none"> <li>• immunosuppressive efficacy</li> <li>• timeliness (in relation to the reversibility of pathology) of treatment</li> <li>• acute and chronic adverse effects attributed to treatment</li> </ul>
Patient (and community) related	<ul style="list-style-type: none"> <li>• ethnicity—eg, genetic variations in the progression of renal failure</li> <li>• geographic variation—eg, healthcare system and local healthcare economics</li> <li>• socioeconomic—eg, access to health services, education</li> </ul>
Others	<ul style="list-style-type: none"> <li>• could be related to disease and/or treatment—eg, long-term vascular disease, malignancy</li> </ul>

circumstances such as social support and education. In this regard, studies from the United States have shown that among White female patients with systemic lupus erythematosus, those who had received education for not more than eight years had a 2.4-fold higher risk of death compared with patients who had >13 years of education.<sup>7</sup> Mechanistic explanations for the relationship between educational level and lupus-related death deserve further studies, but variations in compliance, self-care and monitoring, and other aspects of sickness behavior are likely to be involved.

### Issues Related to Lupus Nephritis

Optimizing treatment of lupus nephritis remains a pivotal issue in the attempt to reduce the morbidity and mortality of patients with systemic lupus erythematosus. The importance relates not only to the prevalence of renal involvement, which affects >50% of patients, but more importantly to the survival disadvantage associated with chronic renal failure. Prevention of renal

failure therefore assumes paramount importance in ensuring long-term survival after treatment of acute disease. Severe proliferative lupus nephritis, which results in rapid nephron loss, is usually treated with a combination of corticosteroid and either intravenous or oral cyclophosphamide, or more recently mycophenolate mofetil.<sup>8–10</sup> We have reported that among Chinese patients with severe proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide induction followed by azathioprine maintenance, 4.6% showed doubling of baseline creatinine during 87 months of follow-up.<sup>11</sup> A subsequent study of 62 Chinese patients with diffuse proliferative lupus nephritis compared oral cyclophosphamide followed by azathioprine with mycophenolate mofetil from induction to maintenance in combination with prednisolone. In this study, 8.1% of the patients demonstrated doubling of baseline serum creatinine during 63 months of follow-up, with similar incidence rates in the two treatment groups.<sup>12</sup> Investigators in the United States have reported doubling of baseline serum

creatinine in 20%–30% of patients with severe lupus nephritis treated with corticosteroid and intravenous cyclophosphamide over 36 months of follow-up, and at 10 years 21.4% of patients had either died or developed end-stage renal failure, while another 11.7% developed chronic renal failure.<sup>8,13</sup> Two of the 62 Chinese patients in our series died during follow-up, one from infection and the other from cerebral hemorrhage.<sup>12</sup> A recent study that included patients of predominantly African or Hispanic origin compared intravenous cyclophosphamide, azathioprine, and mycophenolate mofetil as maintenance therapy following induction with corticosteroid and intravenous cyclophosphamide. In this study, 5 out of 59 patients died and 5 developed renal failure during a median follow-up of approximately three years, with most unfavorable events occurring in patients maintained on intravenous cyclophosphamide.<sup>10</sup>

Data are accumulating on the efficacy of mycophenolate mofetil in severe proliferative lupus nephritis, although long-term data and optimal dosing in non-Chinese subjects remain to be established. The main advantage of mycophenolate mofetil over cyclophosphamide is the much improved safety profile, in particular the reduced incidence of severe infections, which obviously has a direct bearing on patient survival. Mycophenolate mofetil is especially useful during active disease, when potent immunosuppression is most required, and in this case as an alternative to cyclophosphamide. The good tolerance to long-term mycophenolate mofetil treatment blurs the distinction between the induction phase, when the primary aim is to induce remission, and the maintenance phase, when the treatment objective is to prevent relapses, since the drug can initially be used as an induction agent continuing into prolonged maintenance. Nevertheless, the relative efficacy of mycophenolate mofetil com-

pared with corticosteroid alone or in combination with azathioprine as maintenance treatment in the prevention of relapse remains undefined, although such data would be valuable not only clinically but also considering the financial implications. Apart from differences between immunosuppressive regimens, the heterogeneity in renal outcomes reported by different investigators could be related to ethnic variations in treatment response, variations in blood pressure control, and different patient characteristics, including the severity of pre-existing irreversible damage and the rapidity of access to treatment.

Factors that have been reported to adversely affect renal survival in patients with severe proliferative lupus nephritis include a high chronicity index and considerably reduced renal reserve at baseline, failure to achieve complete remission after treatment, repeated nephritic relapses, and uncontrolled hypertension. Favorable long-term renal survival is achievable, despite a high baseline activity index, provided that the irreversible damage is not extensive and the immunosuppressive treatment is effective. In this context, independent investigators have highlighted the importance of achieving remission with induction immunosuppression in order to ensure favorable long-term renal outcome.<sup>14-16</sup> Our own data showed that renal function at last follow-up was associated with baseline renal function and renal function at one year after starting treatment and that the baseline chronicity index was an independent predictor of latest creatinine clearance. Advances in immunosuppressive treatment regimens for lupus nephritis appear to have made a greater impact on severe active disease, when high remission rates are achievable with distinct treatment protocols, though the side-effect profiles may differ significantly. In contrast, up to 40% of patients relapse within 5 years while on low-dose maintenance immunosup-

pression. Until an effective protocol can reduce relapse rate, vigilance to clinical and laboratory indications of impending relapse will be essential so that relapses can be treated early and further attrition of renal reserve can be minimized.

### Long-Term Vascular Complications

As treatment of severe acute manifestations of systemic lupus erythematosus continues to improve, with a decreasing short-term death rate, the importance of preventing long-term complications cannot be overemphasized. Emerging evidence indicates that atherosclerotic vascular complications are assuming increasing importance with regard to long-term illness and late death in patients with a history of lupus despite quiescent disease. Classical risk factors for vascular complications, such as hypertension and hyperlipidemia, are prevalent, affecting more than 40% and 30% of patients, respectively.<sup>17</sup> Different groups of investigators have reported on the increased prevalence of coronary artery calcification and atherosclerotic plaques in patients with a history of systemic lupus erythematosus compared to age-matched controls.<sup>18,19</sup> Furthermore, both the age at the time of diagnosis of lupus erythematosus and the duration of lupus have emerged as independent predictors of atherosclerosis.<sup>18</sup> The interrelationship between systemic lupus, renal failure, and cardiovascular complications remains to be fully elucidated. In view of the established relationship between increased serum creatinine level and cardiovascular events or death in non-lupus subjects, in patients with a history of lupus, the detrimental effects of renal failure in terms of vascular complications could be even more profound. Therefore patients with a history of systemic lupus erythematosus, especially those who have been on long-term corticosteroid therapy or who manifest persistent significant proteinuria from glomerulosclerosis, should be regarded as a high-

risk group for vascular complications and be subject to stringent management of risk factors such as hypertension and hyperlipidemia.

### Psychosocial Issues

Even in the face of continuing improvements in the management of severe lupus and the clinical outcomes, a few patients with disease manifestations amenable to treatment commit suicide.<sup>20</sup> This phenomenon may be related to inadequate understanding of this disease, which could be more of a problem in relatively conservative communities. Education of the public and patients with regard to the reversibility of early disease and the efficacy of treatment can benefit from community involvement.

### CONCLUSIONS

The survival of patients with systemic lupus erythematosus, including those with severe lupus nephritis, has improved considerably over the past few decades, consequent to advances in immunosuppressive therapy and the better management of complications. Further refinement of immunosuppressive or renoprotective treatment regimens is in progress,<sup>21</sup> and the impact of current treatment regimens on long-term renal outcome in different patient populations needs to be better defined. With improvements in treatment efficacy and supportive care, infection-related deaths and vascular complications in long-term survivors remain challenges for clinicians. Future advancements in immunosuppressive protocols via the development of relatively well-tolerated drugs and biologic agents have the potential to maintain or improve immunomodulatory efficacy while reducing treatment-related adverse effects. Despite the continued scientific progress in understanding the pathogenetic and therapeutic mechanisms, and despite the clinical progress in

the formulation of better treatment regimens, the outcome for some ethnic groups remains inferior to that for others, for reasons that may not be purely biological but are likely to involve health financing, politics, and socioeconomic circumstances that directly impinge upon a patient's timely access to health service. The latter factor is particularly relevant to relapsing diseases and those in which early effective treatment is pivotal for a favorable long-term outcome, as exemplified by systemic lupus erythematosus.

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*Design concept of study:* Chan  
*Data analysis interpretation:* Chan  
*Manuscript draft:* Chan  
*Acquisition of funding:* Chan