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# The Evolution of Lupus Activity among Patients with End-Stage Renal Disease Secondary to Lupus Nephritis

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The aim of this study was to evaluate the evolution of lupus activity in end-stage renal disease (ESRD) patients due to lupus nephritis and to determine the long-term prognosis.

We reviewed the clinical courses of 45 patients with ESRD due to systemic lupus erythematosus (SLE). We analyzed the course of SLE following the onset of ESRD, with special attention to the clinical and serological manifestations, survival time on dialysis, and renal transplantation outcome. Disease activity was measured using the SLE Disease Activity Index (SLEDAI).

Of the 45 patients, 21 patients were being treated with hemodialysis (HD), 11 were undergoing peritoneal dialysis (PD), and 13 underwent transplantation. Duration of follow-up was 53 $\pm$ 29 months. The SLEDAI score on commencement of renal replacement therapy was not significantly different among the 3 groups (HD: 4.2 $\pm$ 4.2, PD: 4.3 $\pm$ 2.3, Transplant: 3.2 $\pm$ 1.9). However, disease activity scored by follow-up maximal SLEDAI during dialysis or transplantation showed a significant increase after peritoneal dialysis (HD: 5.0 $\pm$ 3.6, PD: 7.4 $\pm$ 3.7, Transplant: 2.2 $\pm$ 1.7, $p<0.05$). When the individual changes in the maximal SLEDAI score were considered, a significant increase was apparent after peritoneal dialysis ($p<0.05$), but not after either hemodialysis or renal transplantation. There was no significant difference in cumulative survival rate, and also in technique or graft survival rates of the 3 groups. Among the variables tested, follow-up maximal SLEDAI score was the only significant factor associated with patient survival (odds ratio: 1.15, $p<0.05$). The incidence (36% versus 19%) of high disease activity was greater, but not significantly, in the peritoneal dialysis group, as compared to the hemodialysis group. Clinical activity of SLE was apparent in 65% of patients in the first year of dialysis, but none showed any activity after the third year of dialysis.

We found that although lupus disease activity declined after patients progressed to ESRD, lupus disease activity still affected patients' survival. An incremental increase in postdialysis lupus activity was not uncommon, especially during the first one year of dialysis. During the follow-up period, maximal SLEDAI score increased significantly after peritoneal dialysis. However, the long-term prognosis was not significantly different according to the treatment modality.

**Key Words:** Systemic lupus erythematosus, lupus disease activity, end-stage renal disease

## INTRODUCTION

Lupus nephritis develops in 60% of patients with systemic lupus erythematosus (SLE) and is a major cause of morbidity and mortality.[1,2] About 20% of patients with lupus nephritis develop end-stage renal disease (ESRD) within 10 years of its onset.[3,4] Interestingly, the SLE disease activity has been reported to dramatically decline in patients who progress to ESRD.[5-7] This "burn-out" phenomenon of lupus activity was first reported by Fries et al,[5] and was later confirmed by other studies that included patients undergoing hemodialysis.[8,9] However, some reports indicated that disease exacerbations occurred more frequently in lupus patients treated with continuous ambulatory peritoneal dialysis.[10-12] Controversies still exist regarding the outcome of renal replacement therapy, including renal transplantation and the

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specific changes to lupus disease activity during dialysis or transplant.[13,14]

We analyzed the specific course of SLE following ESRD onset, regarding the clinical and serological manifestations, patient survival on dialysis, and the renal transplantation outcome.

## MATERIALS AND METHODS

Between January 1990 and January 2000, 55 patients with SLE, diagnosed by American Rheumatism Association criteria, developed ESRD and were either treated with dialysis or underwent renal transplantation. Medical charts of these 55 patients were reviewed retrospectively to document demographic data and to establish the nature and the severity of the SLE manifestations that characterized the patient's clinical course before and after renal replacement therapy. Since we were interested in the long-term clinical course and prognosis of lupus patients with ESRD, six patients who received dialysis for less than 6 months were not included in this study. However, patients who subsequently received kidney transplantation were included, regardless of the functional status of the transplant. Four patients had to be excluded because of incomplete data.

Disease activities of the remaining 45 patients were measured using the SLE disease activity index (SLEDAI).[15] In this scoring system, high disease activity was defined as an SLEDAI score over 10 points. High non-renal disease activity was determined as a score over 10 points that was calculated from SLEDAI items other than renal disease, for example, proteinuria, or hematuria. The SLEDAI score was calculated before and at least every year after the development of ESRD, and clinical activity and serologic markers were analyzed likewise. Follow-up maximal SLEDAI score was determined as the largest SLEDAI score observed during follow-up. SLE clinical activity was judged to be present if one or more of the following was observed: malar rash, oral ulcers, alopecia, arthritis, myositis, pericarditis, pleuritis, fever, cerebritis, or vasculitis. Myositis was defined as proximal muscle aching or weakness, associated with elevated creatinine phosphokinase or electromyogram changes; arthritis, as more than two joints with pain and signs of inflammation; cerebritis, as seizure or psychosis; and vasculitis as ulceration, gangrene, tender finger nodule, or splinter hemorrhages. Serologic tests for lupus activity included leukocyte counts, platelet counts, antibodies to double-stranded DNA, and serum complement 3 (C3) levels. We also reviewed daily dosages of prednisolone, and use of immunosuppressive agents.

### Statistical analysis

Comparisons among hemodialysis, peritoneal dialysis, and kidney transplantation groups were performed using one-way ANOVA tests for continuous variables with normal distribution, and chi-square tests for categorical variables. SLEDAI scores were compared using Wilcoxon's signed-rank test. Kaplan-Meier survival analysis was used to compare the probabilities of technique or graft failure and patient mortality. Significance was assigned at the $p<0.05$ level, all hypotheses were two-tailed.

## RESULTS

### Baseline characteristics

Demographic characteristics and the clinical course of SLE following ESRD onset are shown in Table 1. Of the 21 out of 45 patients who received hemodialysis, 11 had peritoneal dialysis, and 13 underwent renal transplantation. This predominantly female (72%) population was much younger than the general dialysis population. Mean follow-up period was 53 ± 29 months. 10 renal allograft patients had a living-related transplant, and three had a living-unrelated transplant. Transplant recipients received dialysis treatment for at least 3 months (3 to 48 months) before transplantation. Prior to transplantation, 10 patients underwent hemodialysis and 3 patients had peritoneal dialysis. Renal allograft patients were observed for an average of 45 months of functioning graft (range 3-84 months).

Hemodialysis, peritoneal dialysis, and trans

**Table 1.** Demographic Characteristics of Patients

| | HD | PD | Transplantation |
|---|---|---|---|
| Number of patients (M:F) | 21 (4:17) | 11 (2:9) | 13 (4:19) |
| Age at diagnosis of SLE (years) | 28 ± 9 | 31 ± 8 | 24 ± 8 |
| Time from diagnosis of lupus nephritis to ESRD (months) | 26 ± 22 | 39 ± 48 | 32 ± 18 |
| Age at diagnosis of ESRD (years) | 31 ± 9 | 36 ± 10 | 31 ± 8 |
| Follow-up period since ESRD (months) | 55 ± 42 | 50 ± 39 | 42 ± 28 |
| SLEDAI score before dialysis or transplantation | 4.2 ± 4.2 | 4.3 ± 2.3 | 3.2 ± 1.9 |
| Follow-up maximal SLEDAI score during dialysis or transplantation | 5.0 ± 3.6 | 7.4 ± 3.7[a] | 2.2 ± 1.5 |
| Daily dosage of prednisolone at diagnosis of ESRD (mg) | 15.3 ± 8.2 | 13.9 ± 7.8 | 14.3 ± 9.7 |
| Daily mean dosage of prednisolone during dialysis or transplant (mg) | 5.3 ± 3.2 | 4.8 ± 2.5 | 9.6 ± 2.5[b] |

M, male; F, female; ESRD, end stage renal disease; HD, hemodialysis; PD, peritoneal dialysis.
[a]$p<0.05$ for PD vs HD and PD vs transplantation, in Post Hoc test.
[b]$p<0.05$ for Transplantation vs HD and transplantation vs PD, in post Hoc test.

**Table 2.** Number of SLE Patients with High (SLEDAI > 10 points), Low (SLEDAI: 1 to 10 points) or No (SLEDAI: 0 point) Disease Activity before and during Dialysis or Transplantation

| Nonrenal disease activity before RRT | Overall maximal disease activity during RRT | | |
|---|---|---|---|
| | SLEDAI: 0 | SLEDAI: 1-10 | SLEDAI: > 10 |
| SLEDAI: 0 (n=3) | 2 | 1 | 0 |
| SLEDAI: 1-10 (n=40) | 5 | 29 | 6 |
| SLEDAI: > 10 (n=2) | 0 | 0 | 2 |

RRT, renal replacement therapy.

plant patients all showed similar mean age of SLE onset, time from SLE diagnosis to ESRD onset, and mean duration of follow-up after ESRD onset. The number of patients using high-dose prednisolone (greater than 30 mg/day), and immunosuppressants was not significantly different according to the treatment modality (data not shown).

## SLE activity in ESRD

Among whole patients, high disease activity before renal failure occurred in 34 patients (76%), while high non-renal disease activity occurred in only 14 of all patients (31%). However, high disease activity by SLEDAI score on commencement of renal replacement therapy was observed in only 2 of all patients (4%). In the majority, renal failure progressed despite clinical quiescence of lupus activity by all criteria other than renal disease itself.

Table 2 shows comparisons of the number of patients with high, low, and absent disease activity before and after undergoing more than 6 months of dialysis or transplantation. The number of patients with high disease activity and absent disease activity increased, but the number of patients with low disease activity slightly decreased.

Disease activity by the SLEDAI score on commencement of dialysis or transplant was not significantly different among the 3 groups, but disease activity by follow-up maximal SLEDAI score increased significantly after peritoneal dialysis ($p<0.05$; Table 1). Taking into consideration the individual changes in maximal SLEDAI score, after peritoneal dialysis there were significantly more increased cases ($p<0.05$; Fig. 1), compared to hemodialysis and renal transplantation. The incidence (36% versus 19%) of high

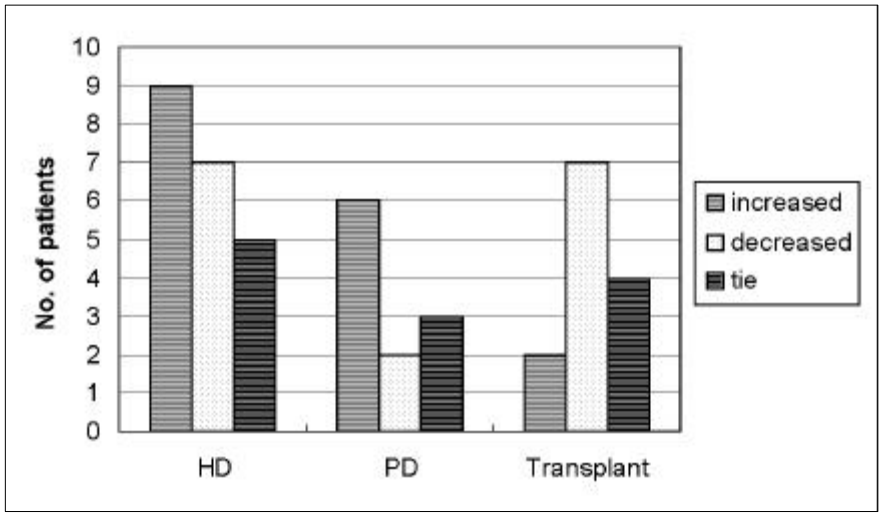


**Fig. 1.** The change of follow-up maximal SLEDAI score per patient during renal replacement therapy compared to the score before the therapy. The individual changes in maximal SLEDAI score were significantly more increased in cases after peritoneal dialysis ($p<0.05$), compared to hemodialysis and renal transplantation.

**Table 3.** Disease Activity of SLE after the Onset of ESRD

| | Years after onset of ESRD | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 5 |
| No of patients | 33 | 29 | 24 | 16 |
| SLEDAI score | 5.2 ± 4.9 | 3.2 ± 2.7 | 2.9 ± 2.8 | 2.1 ± 1.9 |
| Clinical activity (%) | 65 | 30 | 13 | 0 |
| Serological activity (%) | 80 | 60 | 52 | 15 |

disease activity during follow-up was also greater in the peritoneal dialysis group, compared to the hemodialysis group, although this was not statistically significant (p=0.57; data not shown). High disease activity was not seen in the transplant group.

Serological lupus parameters remained active in the majority of patients before and after developing ESRD. Serological markers were positive in 80%, 60%, and 52% of these patients in the first, second, and third years of dialysis, respectively. On the other hand, clinical SLE activity was apparent in 65% of patients in the first year, but none showed any activity after three years. Although serological activity continued in a small fraction of patients into the fifth year, in most patients clinical activity of lupus was already negligible after the third year of dialysis. The loss of clinical activity preceded the loss of serological activity (Table 3).

**Survival of SLE patients on dialysis or renal transplantation**

During the follow-up period, 13 patients expired due to infection (6 patients), lupus disease flare (4 patients), and cardiovascular disease (3 patients). Four out of 7 patients who died within one year of ESRD had high SLE disease activity at the time of death. Cumulative patient survival rates after the onset of ESRD were 81%, 72%, and 68% at 2, 5, and 10 years, respectively.. No significant difference in the cumulative survival rate was found among the 3 groups ($p$=0.44; Fig. 2). When we analyzed the influence of age over 30 years and short duration of renal disease (less than 12 months) before dialysis or transplantation, we found that these factors had no impact on subsequent survival with dialysis. The unadjusted risk of patient mortality was 2.35 times greater for men than women, and this increased by 6% with each point of the SLEDAI score before renal

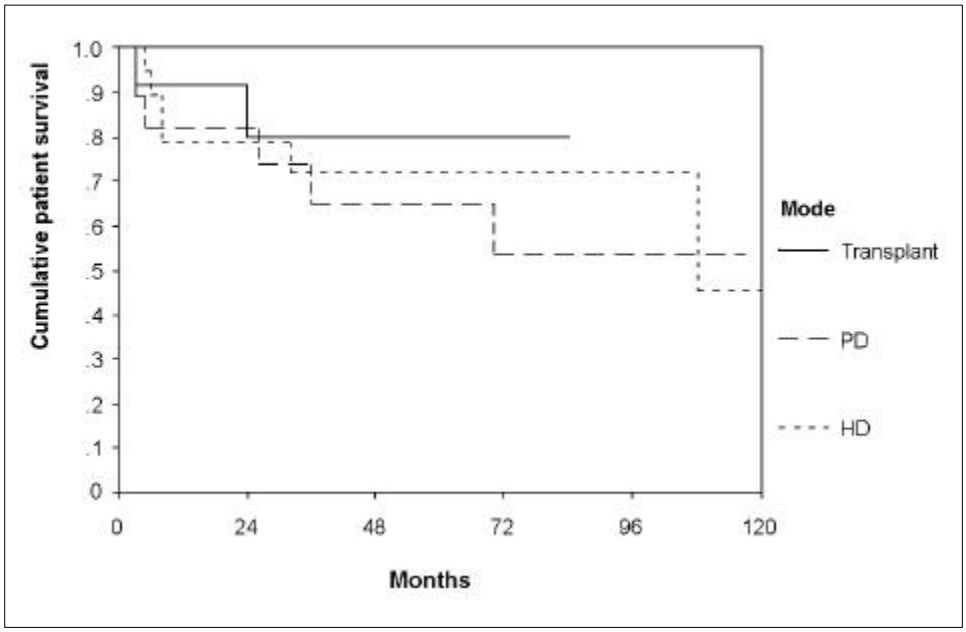


**Fig. 2.** Patient survival according to the treatment modality.

replacement therapy, and by 19% with each point of the follow-up maximal SLEDAI score. However, after adjusting for potentially confounding variables, the risk of patient mortality increased significantly by 15% increments with each score of the follow-up maximal SLEDAI score (95% CI, 1.07 to 1.21, $p<0.05$).

Technique or graft survival rate was 81% at 5 years, and the difference of technique or graft survival rate was not statistically significant among the 3 groups ($p$=0.37, HD: 83%, PD: 85%, and Transplant: 75% at 5 years). For up to 84 months of follow-up, none developed a clinically apparent recurrence of lupus nephritis. Biopsy was performed in 7 cases. None of the transplanted kidney tissue specimens showed any pathological characteristics of SLE.

## DISCUSSION

The development of renal disease has a major prognostic impact upon patients with SLE. The incidence of ESRD due to lupus nephritis has increased, despite the introduction and the recognition of efficacious new treatment regimens, particularly cytotoxic medications.[1] The course of SLE after ESRD onset has been studied by several groups.[5-13] In the majority, non-renal clinical SLE activity appeared to decrease following progression to ESRD, and this contention was supported by the concurrent decrease in normal immunologic functions found in patients with ESRD. These changes included granulocyte dysfunction, decreased T-helper cell numbers, and decreased lymphocyte activation.[16,17] However, it is still uncertain whether this "burn-out" of SLE disease activity is due to the uremic state or to the natural disease course of SLE.

Investigations of disease course are fraught with difficulties, especially with respect to uremia: i.e., what should be considered as SLE disease activity, and what should be attributed to renal failure or to dialysis; which end points should be used for SLE, knowing that it is a chronic disease that shows exacerbation and remission, characteristics which vary from patient to patient. We analyzed lupus disease activity by determining the follow-up maximal disease activity, as assessed by the SLEDAI score, and compared these parameters in all patients before and during dialysis or transplant.

We found differences in the individual changes of follow-up maximal disease activity, according to the treatment modality. The bases of these differences in clinical and serological lupus activities between hemodialysis and peritoneal dialysis are unknown. Some mechanisms have been postu-

lated to account for the differences in immune reactivity. First, Lonnemann et al.[18] showed possible mechanisms involved in hemodialysis-associated cytokine induction: adherence of mononuclear cells to the dialyzer membrane; complement activation by the dialyzer membrane, and the passage of cytokine-inducing bacterial fragments from contaminated dialysate through the dialyzer membrane into the blood. Second, phagocytosis was preserved in patients receiving peritoneal dialysis, whereas it was significantly impaired in patients receiving hemodialysis.[19] Third, the enhanced removal of middle molecules (uremic toxins of molecular weight 300 to 2,000 Daltons) by peritoneal dialysis could also be responsible for this difference. Compared to hemodialysis, middle molecule clearance is six times greater in peritoneal dialysis,[20] and it may modulate some of the immunosuppressive effects of uremia. Increments of increased post-dialysis lupus activity, particularly during the first year of peritoneal dialysis, are common. Grzegorzewska et al.[21] demonstrated that after 6-12 months of peritoneal dialysis there was a significant increase in total lymphocyte count and CD4:CD8 ratio. However, after the first complete year of peritoneal dialysis, total lymphocyte counts, CD3, CD4, CD8, and CD19 cell counts decreased; and in patients on peritoneal dialysis for more than 36 months, CD3, CD4, CD8, and CD19 cell counts were below the normal range. Prolonged use of the low pH and high lactate peritoneal dialysis solutions are also detrimental to the normal peritoneal immune defences.[22]

In the present study, lupus activity was found to be greater than that reported in previous studies. Our data were collected by a retrospective chart review with a bias toward including any symptoms that might represent SLE, and this could potentially have over-represented disease activity. Several of the events used in the index, such as pericarditis or pleuritis, may have occurred because of either active lupus or complications associated with uremia or dialysis. Fever, a more common event, could have been erroneously attributed to lupus activity, rather than an infectious cause. Despite these problems that might have resulted in overestimating SLE activity, serological data, which is a more objective measurement of disease activity, provided clear evidence of lupus activity in our patients. In addition, we found a male to female ratio of 1 : 3.5 in our dialysis or transplant-treated patients, which compared with an overall male to female ratio of 1 : 10 in SLE. This might be regarded as another argument that male patients with SLE suffer more severe renal disease.

In the present study, patient survival rate on long-term dialysis was excellent. Other investigators,[8,17] but not all,[6] have reported similar results. The favorable outcome for lupus patients undergoing dialysis might result from other characteristics of the patient population, such as their youth and the quiescent lupus activity. Pollack and Ibels observed that old age, male gender, and a rapid progression of renal failure with clinical lupus activity were all associated with lower survival rates.[23]

The SLEDAI score before initiation of dialysis or transplantation was not shown to be a risk factor for patient survival. The reason was not clear, although it might be due, in part, to an improved abnormal immune response after renal replacement therapy. Initiation of dialysis treatment leads to improved T-cell activation in patients with end-stage renal disease,[21,24] which may lead to increased disease activity. Szeto et al.[14] also reported that active lupus at the initiation of dialysis did not predict future activity.

In our study, the risk of patient mortality increased significantly by 15% with each increment in the follow-up maximal SLEDAI score. The persistent lupus activity as an important factor might be due to corticosteroid therapy, which could have contributed to development of sepsis, cardiovascular complications, and eventual patient death. This evidence may suggest that disease activity after the initiation of renal replacement therapy might be more important in determining patient survival.

In the present study, 13 patients received kidney transplantation. After transplantation, lupus activity continued to decrease compared to the predialysis and dialysis periods. However, this change in lupus activity was not significantly different, probably because of the low statistical power. Both patient and graft survival rates were excellent.

During the follow-up period, 13 patients died, 6 from infections, 4 from active SLE, and 3 from cardiovascular disease. However, other reports indicate that infectious and cardiovascular diseases are the most common causes of death in lupus dialysis patients,[2,8] but active SLE was not. According to our results, major mortality causes consisted of infection and active SLE, and all 4 patients with active SLE died within one year of ESRD. Therefore, the present study shows that lupus activity might persist for several years in patients with ESRD. The extent of steroid therapy, as well as clinical lupus activity, appeared to determine the prognosis and the quality of life of these patients. The small number of patients involved in our study limited its statistical power. The factors we found to be associated with patient survival can only serve as indicators for further research, rather than be viewed as conclusive evidence in their own.

In summary, we found that lupus disease activity declined after patients progressed to ESRD, but still affected their survival. An increment in postdialysis lupus activity was not uncommon, especially during the first complete year of dialysis. SLE patients on dialysis should be carefully followed up by clinical and serological monitoring, and treated by appropriate immunosuppressive therapy.

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