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Improving Outcomes in Patients with Lupus and End Stage Renal Disease

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Abstract

The development of lupus-related end stage renal disease (ESRD) confers the highest mortality rates among individuals with lupus. Lupus-related ESRD is also associated with higher morbidity and mortality rates compared with non-lupus ESRD.

We review the evidence that persistent lupus activity, hypercoagulability, and continuing immunosuppression may contribute to unfavorable outcomes in dialysis and renal transplantation among lupus patients. Robust epidemiologic studies are needed to develop individualized evidence-based approaches to treating lupus-related ESRD.

In the meantime, managing lupus-related ESRD presents a significant challenge for clinicians and requires a team approach involving nephrologists and rheumatologists. Goals of therapy after developing ESRD should include continuing monitoring of lupus activity, minimizing corticosteroid exposure, and choosing the most appropriate renal replacement therapy based on patient's risk profile and quality of life considerations.

Kidney involvement due to lupus nephritis is one of the leading causes of morbidity and mortality in systemic lupus erythematosus (SLE). Among patients with lupus, nephritis is more frequent in men compared with women, and in African-Americans and Hispanics compared with Caucasians[1, 2]. Lupus nephritis develops early in the course of the disease and is observed in up to 60% of SLE patients in the United States[3]. Ten to 30% of these individuals progress to end stage renal disease (ERSD) despite aggressive immunosuppressive therapy[4].

SLE-related ESRD is associated with higher morbidity and mortality rates compared with non-SLE ESRD. Sule et al.[5, 6] examined mortality rates and hospitalization rates among 1,341 SLE ESRD and 93,694 non-SLE ESRD, reported by the 2006 United States Renal Data Systems (USRDS). Infections and cardiovascular disease were the leading causes of hospitalizations and mortality among both SLE and non-SLE ESRD. However, adult SLE ESRD patients were hospitalized more frequently, had longer hospitalizations, and had higher age-, sex- and race-adjusted mortality rates compared with non-SLE ESRD.

The development of ESRD also confers the highest mortality rates among SLE patients. A recent single-center study from Hong Kong by Yap et al.[7] reported that the standardized mortality ratios (SMR) among 208 patients with biopsy-proven lupus nephritis not requiring

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dialysis was 5.9, compared with 26.1 for those with ESRD. Importantly, no differences in SMR were found when patients were stratified according to the decade of presentation between 1968 and 2008. Similarly, Costenbader et al.[4] examined USRDS data in 12,344 individuals with incident SLE-related ESRD for 1995 - 2006, and found no change in SMRs during this 12-year study period. Although neither of these two studies compared relative SMR rates and trends for SLE-related ESRD and non-SLE ESRD, USRDS data do show a steady decline in mortality rates in hemodialysis patients since the 1990s[7]. As discussed below, we believe that SLE-specific factors may account for the failure of SMR to improve for ESRD patients with SLE undergoing renal replacement therapy (RRT).

Disease activity in SLE ESRD patients

There is a common perception among rheumatologists that SLE becomes clinically inactive after ESRD develops, due to immune system alterations associated with uremia and ESRD. Despite this common perception, robust experimental and epidemiologic data are lacking.

ESRD is associated with complex alterations of innate and adaptive immunity contributing to accelerated atherosclerosis and increased susceptibility to infection[8]. On the one hand, ESRD is associated with increased macrophage activation, increased oxidative stress, and up-regulation of inflammatory cytokines[9]. On the other hand, there is decreased monocyte and neutrophil function and immune deficiency caused by depletion of dendritic cells, B cells and T cells[8].

ESRD-associated immune alterations may also modulate disease activity in SLE by several mechanisms. First, B cell survival is reduced in ESRD. This is associated with an increased resistance to B-cell activating factor (BAFF), down-regulation of BAFF receptors[10], and increased B-cell apoptosis[8]. BAFF is a member of the tumor necrosis factor family of cytokines that drives B cell differentiation, proliferation and survival. BAFF plays an important role in the pathogenesis of SLE. BAFF is up-regulated in SLE, and BAFF inhibition reduces the frequency and severity of lupus flares when added to standard immunosuppressive therapy[11]. However, there are no studies examining the role of BAFF in ESRD patients with SLE. Second, decreased T-cell production in ESRD is associated with a shift from Th2 toward Th1 responses, which may lead to immunosuppression and decreased autoantibody production in SLE patients[12, 13]. Again, the significance of these alterations in SLE patients with ESRD has not been explored.

To date, there are no prospective clinical studies evaluating disease activity in SLE after the onset of ESRD. Mattos and Santiago[14] reviewed 24 retrospective studies that were published between 1973 and 2011. Fifteen studies observed a substantial reduction in clinical and/or serological activity of SLE after the onset of ESRD, while 9 others concluded that disease activity persisted unabated after the onset of ESRD. In several studies, it appeared that most SLE flares occurred in the first year of RRT[15–17]. Most of the studies included in this systematic review were retrospective case series consisting of 6–59 patients with heterogeneous definitions of disease and variable duration of follow-up. Furthermore, no adjustments were made for patient demographics, co-morbid conditions, renal replacement modality or administered medications. Only 14 of these studies evaluated disease activity before and after the onset of ESRD, while the rest of the studies evaluated disease activity only after ESRD onset. Therefore, changes in disease activity observed in some of these studies may have reflected the natural course of SLE, since these studies lacked non-ESRD SLE control groups for comparison[18]. These limitations, together with possible publication bias, make these data very difficult to interpret.

One of the major challenges in studying SLE activity in ESRD is that there are no validated measures of disease activity in ESRD. Some of the components of the current scoring

systems used to gauge SLE activity, such as fevers, serositis, seizures, low serum complement levels and cytopenias may occur in hemodialysis patients without SLE[19]. Furthermore, serologic markers of SLE activity, such as complement levels and anti-dsDNA antibodies, do not strongly correlate with non-renal clinical disease activity, morbidity or mortality in SLE patients with ESRD[18, 20].

We performed a retrospective chart review of 80 SLE ESRD patients followed in our institution between 2001 and 2006 and found that SLE ESRD patients who were treated with immunosuppressive medications with or without prednisone had significantly better survival than patients who were not treated or treated with prednisone alone. This finding remained unchanged after adjusting for age, sex, transplantion status, and the frequency of rheumatology visits after the development of ESRD. While we did not have complete information on disease activity and there were several potential biases related to the retrospective nature of this study, our data suggest that undertreatment of active SLE after the onset of ESRD may contribute to decreased survival[21].

By implication, then, active SLE in ESRD patients may be missed or misdiagnosed in clinical practice and therefore under-reported in clinical studies. Consequently, undertreatment of active SLE may contribute to higher rates of cardiovascular disease and vascular access thrombosis in lupus patients undergoing maintenance hemodialysis as compared to the general population of dialysis patients. Some of these possible associations are discussed below.

Antiphospholipid antibodies and thrombosis in ESRD

Vascular access failure is one of the leading causes of morbidity, mortality and hospitalizations in ESRD[22]. It is not clear that SLE patients are at a higher risk for vascular access complications though the one study on the subject suggests it. That retrospective study compared rates of vascular access thrombosis in 36 SLE patients and 36 non-SLE controls, matched for age, sex, race and vascular access and found a 66.6% rate in SLE compared with 38.9% in non-SLE patients (OR 3.1,95%CI 1.2–8.2). This study did not identify the factors predictive of vascular access thrombosis in lupus patients[23].

While vascular access complications are multifactorial and related to both genetic and acquired factors, one possible mechanism of increased vascular access thrombosis in SLE may be the presence of antiphospholipid antibodies (aPL Abs). aPL Abs are a heterogeneous group of Abs directed against phospholipids (such as cardiolipin) or phospholipid-binding proteins (such as β2-glycoprotein I or annexin A5). Over 30% of SLE patients develop persistently positive aPL Abs during the course of their disease. Persistently positive aPL Abs are associated with an increased risk of arterial and/or venous thrombosis, as well as complications during pregnancy. While this condition, known as antiphospholipid syndrome, may occur in individuals without SLE, it occurs with a higher frequency in SLE patients. Although aPL Abs may be present for a long time before an acute thrombotic event, it is widely accepted that they play an active role in the pathogenesis of antiphospholipid syndrome[24, 25]. However, not all aPL Abs are pathogenic, and some may merely reflect endothelial damage in inflammatory states such as SLE and ESRD [26, 27].The exact mechanisms of thrombosis in antiphospholipid syndrome are not well understood.

Several studies reported that aPL Abs are present in 15–30% of non-SLE ESRD, and that aPL Abs are associated with an increased risk of vascular access thrombosis and mortality in non-SLE ESRD dialysis patients, and graft failure in non SLE renal transplants (RT)[28] (also, previously reviewed by Joseph et al.[29]). This reported prevalence of aPL Abs in non-SLE ESRD is much higher than the 5% prevalence reported in the general population[30]. Surprisingly, there are no studies to date specifically evaluating any association between

aPL Abs and vascular access thrombosis in SLE patients undergoing hemodialysis. It remains unclear how to best manage aPL positive individuals with ESRD. There are no proven preventive treatments that can decrease the risk of developing thrombosis in asymptomatic patients with aPL Abs (primary prevention). Anticoagulation is recommended for preventing recurrent thrombosis in patients with antiphospholipid syndrome (secondary prevention). However, anticoagulation is associated with an increased risk of bleeding, especially in ESRD patients, and it is unclear how effective anticoagulation is in preventing thrombotic events in this population[31].

In recent years there has been emerging evidence suggesting that hydroxychloroquine, a drug that is widely used to treat SLE, may be beneficial in decreasing thrombosis risk in aPL positive patients. Hydroxychloroquine use is associated with the lower rates of SLE flares, lower risk of end organ damage, better overall survival, and low rates of thrombosis in SLE patients[32–34]. Some experimental evidence suggests that hydroxychloroquine may decrease the risk of thrombosis by protecting the annexin A5 “anticoagulant shield” on vascular endothelial cells from being disrupted by aPL-beta2-glycoprotein I complexes[35, 36]. In addition, hydroxychloroquine may reverse platelet activation by aPL Abs[37]. However, there are no studies exploring the role of hydroxychloroquine in modulating disease activity or in preventing thrombosis in the dialysis population.

Understanding the relationship between SLE, aPL Abs and ESRD, may help risk stratify patients who are at greatest risk for vascular access thrombosis. This information could provide an additional insight into selecting the renal replacement modality that is most appropriate for these patients.

Choosing the most appropriate renal replacement modality

As with non-SLE ESRD population in the United States, home-based dialysis modalities are underutilized for lupus patients with ESRD. According to USRDS data, of the 11,317 individuals with incident SLE-related ESRD between 1995 and 2006, 82.0% initiated HD, 12.2% initiated peritoneal dialysis (PD), and 2.8% underwent pre-emptive RT[38]. Whether or not outcomes are comparable for lupus patients who undergo HD versus PD has not been well studied.

There are several retrospective studies that report that lupus patients on PD have worse outcomes than other patients on PD or lupus patients receiving HD. PD therapy was associated with lower albumin levels and higher rates of exit-site infections and peritonitis. These factors were associated with high PD dropout rates and mortality[39–41]. However, data from other studies show comparable survival between PD and HD in lupus patients[42–45]. Moreover, the relationship between dialysis modality and outcome in lupus ESRD may be confounded by gender. One of the largest and most recent retrospective studies collected data from 1073 SLE ESRD patients in Taiwan who started maintenance dialysis between March 1997 and December 2006[44]. While men had poorer outcomes on HD than on PD, outcomes in women did not differ based on dialysis modality[44].

Transplant outcomes in SLE patients may also differ based on pre RT dialysis modality. Tang et al [46] utilized USRDS data to identify factors associated with better transplant outcomes in 2882 SLE ESRD patients transplanted between January 1995 and December 2002. Pre-transplant PD was associated with a substantially lower risk of graft failure compared with HD (HR 0.49, 95% CI: 0.34, 0.70, $p < 0.001$). The authors suggested that this may in some way be related to better preservation of, residual renal function by PD (as with non-SLE ESRD[47]), and that HD may give rise to more frequent post transplant infections and increased sensitization in transplant candidates due to factors related to vascular access related factors and exposure to artificial dialysis membranes[48, 49].

In both SLE and non-SLE populations, the association between dialysis modalities, transplantation outcomes, and mortality should be interpreted with caution due to the inherent "confounding by indication" bias related to the retrospective nature of these studies[50]. (Confounding by indication is a common bias in epidemiologic studies that occurs when different treatments are intentionally chosen for patients with different prognosis[50]). In the case of renal replacement therapy in SLE-related ESRD, the initial choice of therapy may depend on many factors that can ultimately affect outcomes. Numerous studies have shown that there are significant demographic, socio-economic and laboratory differences between individuals receiving initial PD compared to those receiving initial HD[38, 50]. More discriminating statistical approaches, such as careful matching, propensity scores, and the instrumental variable method[50] may be needed to evaluate the effects of dialysis modality on outcomes in lupus patients and perhaps identify those patients in whom PD offer particular advantages.

Renal transplant in SLE

In 1975, the American College of Surgeons/National Institute of Health (ASC/NIH) Transplant Registry reported that patient and allograft survival among 56 lupus renal transplant recipients were comparable to non-lupus renal transplant recipients at 2-year follow-up[51]. Since then, renal transplant has been accepted as a viable treatment option for ESRD in patients with lupus. There are also data suggesting that pre-emptive RT in SLE is associated with better outcomes[52] As with non-SLE ESRD, RT is associated with significantly better patient survival than continued dialytic therapy[42]. Although some studies report higher SLE recurrence rates in living donor transplants [53, 54], most studies find that living donor transplants are associated with better outcomes compared with cadaveric transplants[42, 46]. The reported prevalence of SLE recurrence after RT varies widely, between 2% and 54% (recently reviewed by Canaud et al[55]). While biopsy proven recurrence was reported in up to 54% of SLE RT undergoing surveillance renal biopsies[53], most lesions were mesangial (class I or II according to the ISN/RPS Classification of Lupus Nephritis[56]), and clinically significant recurrence leading to active disease and allograft loss was reported in only 2%-11% of SLE RT[54, 57].

While many studies show comparable outcomes in SLE RT and non-SLE RT [58–60], others show slightly higher rates of graft rejection and mortality in SLE RT, both long-term and short-term [61–63]. As with other retrospective studies discussed above, these findings may be influenced by several potential biases, including confounding by indication, and significant age differences between SLE and non-SLE RT patients.

There are several additional SLE-specific issues that may affect outcomes in SLE RT. First, there is no consensus regarding the optimal timing of renal transplantation for SLE patients. Some experts suggest that RT be considered only after patients achieve sustained clinical remission for 6 to 12 months[64]. Second, aPL Abs may be associated with unfavorable outcomes in RT in SLE patients, leading to an increased risk of allograft loss, recurrence of aPL related kidney lesions, and increased mortality[18, 29], especially among patients with antiphospholipid syndrome [65–67]. Third, Norby et al.[68] reported that 67% of deaths among 77 SLE RT were due to cardiovascular disease compared to 40% among non-SLE RT matched for age, sex, date of transplant and donor source (living vs. deceased). As is the case in the non-SLE RT population, aggressive primary and secondary prevention of cardiovascular disease may lead to improved outcomes[69], although high rates of cardiovascular disease observed in SLE RT could be due, in part, to corticosteroid use and SLE disease burden prior to reaching ESRD. Lastly, it is not known whether transplant-related immunosuppression contributes to the better outcome seen in SLE RT patients as

compared to those SLE patients who continue to undergo HD. Certainly the effect of this immunosuppression on SLE activity comes at no additional risk and likely is advantageous.

Disease management considerations in lupus-related ESRD

In the absence of good epidemiologic studies, managing SLE-related ESRD poses a significant challenge for clinicians. Below we provide several suggestions based on our experience and based on the review of the current evidence.

A team approach involving rheumatologists and nephrologists will achieve the best outcomes. Patients should continue to follow-up with a rheumatologist at least twice a year to monitor lupus activity and to adjust medications[21]. After initiation of chronic dialysis, aggressive immunotherapy that was based on a renal indication is no longer warranted; non renal considerations should determine the dosing of these drugs. Serologic markers of disease activity do not correlate well with clinical disease activity in ESRD. Nevertheless, these markers have value and should be measured. Patients with significant changes in serum complement levels or anti-dsDNA levels may need closer monitoring and a slower taper off corticosteroids. This decision should be based on both the severity of extra-renal manifestations and stability of serologic markers of disease activity[32]. Adrenal insufficiency is a potential consideration in these patients, and stress dose steroids should be administered in accordance with the current recommendations for patients on chronic corticosteroids[70, 71]. We believe it is particularly important that SLE ESRD patients receive immunizations in accordance with current recommendations[72, 73].

Though safety data are limited, several immunosuppressive treatments appear quite useful to reduce corticosteroid use and treat extra-renal manifestations of SLE in ESRD. Hydroxychloroquine has a favorable side effect profile, and may improve outcomes in lupus patients with ESRD by decreasing risk of flares and thrombotic complications[32]. However, the risk of hydroxycholoquine-associated retinal toxicity may be increased in ESRD patients, and may require more frequent monitoring[74].

Rituximab can be used in HD patients with no dosage adjustment; it is not eliminated by HD [75, 76]. Cyclosporine and low-dose azathioprine may be used in ESRD as needed to manage extra-renal manifestations with close monitoring of for hematologic and liver toxicity. Cyclophosphamide is used to treat life-threatening severe manifestations of SLE, including neuropsychiatric lupus. ESRD patients have a reduced systemic clearance of cyclophosphamide and a prolonged elimination half-life. Therefore, dose adjustments need to be made. However, hemodialysis eliminates about half of the drug present; a 3 hr dialysis given seven hours after an 1 hr cyclophosphamide infusion removed 22% of the drug[77]. Additional data on safety and dosing of rituximab, cyclosporine, and cyclophosphamide in ESRD are available from the literature published on treatments of other conditions including vasculitis, rapidly progressive glomerulonephritis, and Goodpasture syndorome[78–82].

Intravenous immunoglobulin (IVIG) has been used in kidney transplantation for decreasing reactive antibodies in highly sensitized patients and for treating antibody mediated rejection [83, 84], and can be used in SLE ESRD. Metabolism of mycophenolate mofetil (MMF) is impaired in dialysis patients and may be associated with the poor gastrointestinal tolerance. Thus, dose adjustments are needed and the evaluation of therapeutic plasma concentration of mycophenolic acid is recommended in dialysis patients[85]. The use of methotrexate is not recommended in ESRD as it could cause severe bone marrow suppression and neutropenia in these patients[86].

Patients with antiphospholipid syndrome may need to continue anticoagulation therapy after ESRD onset to prevent further thrombotic complications[32, 87], although patients with CKD

(eGFR less than 30 mL/min per 1.73 m^2) have a 2-fold risk of major hemorrhage compared with patients without renal impairment[88]. SLE ESRD patients should be screened for the presence of antiphospholipid antibodies. Individuals with persistently elevated antiphospholipid antibody levels may have a higher risk of vascular access complications thus favoring, to some extent, the choice of peritoneal dialysis compared with hemodialysis. Individuals with antiphospholipid syndrome and recurrent thrombotic complications despite anticoagulation are not good candidates for kidney transplantation[65–67].

In 1989 Rogby published one of the first reviews addressing several issues related to disease activity and patient management in lupus-related end stage renal disease[89]. In 1998 Stone identified several important gaps in our understanding of the unique issues related to lupus patients undergoing RRT and highlighted methodological problems inherent in addressing these issues[18]. Surprisingly, very little progress has been made since 1989 in developing evidence-based approaches to treating SLE-related ESRD patients. There are multiple challenges in studying SLE ESRD. Disease activity is difficult to define and capture. In addition, disease course and severity vary widely among individuals, as do flare rates. . Moreover, disease course varies before and after ESRD develops, making it a challenge to select appropriate control groups. Randomized trials to address many of these issues are not feasible, at least at this time Therefore, innovative use of existing databases and large registries and design of sound multidisciplinary studies are important goals.

In conclusion, ESRD, a common complication of SLE, is responsible for much of the increased morbidity and mortality in this disease. SLE-related ESRD is associated with worse outcomes compared to other causes of ESRD, and there has been no decline in SLE-related ESRD mortality despite advances in renal replacement therapies in recent years. Therefore, it is important to understand and manage SLE-specific factors (including disease activity, hypercoagulability, and immunosuppression to improve outcomes in SLE-related ESRD. Understanding the natural history and mechanisms of disease activity in SLE-related ESRD may help elucidate new approaches to induce and maintain disease remission, and to improve outcomes. Finally, understanding the contribution of aPL Abs to vascular access thrombosis and renal allograft failure may lead to new therapeutic approaches and improved outcomes in both SLE and non-SLE ESRD.

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