

Kidney transplantation in patients with systemic lupus erythematosus

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Abstract

Despite improvements in overall prognosis in lupus nephritis, 10%-30% of patients with proliferative renal involvement progress to end stage renal disease, according to the severity of the disease and associated socioeconomic factors. Kidney transplantation has been recognized as the most appropriate treatment for those patients, but several issues remain after renal function restoration in a lupus recipient. Among these are the fear of lupus nephritis recurrence in the graft, the choice of immunosuppressive therapy in cases of recurrent lupus for a patient who has already received a toxic and prolonged immunosuppressive course, and finally, the management of comorbidities to reduce associated morbidities in the long term. All the above topics are examined in this review, with the hope of providing a clear picture of data as illustrated in the current literature.

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Key words: Kidney transplantation; Lupus; Recurrence

Core tip: Significant improvement has been made in the management of lupus nephritis, but 10%-30% of patients with proliferative renal involvement still progress to end stage renal disease, according to the severity of the disease and associated socioeconomic factors. Kid-

ney transplantation has been recognized as the most appropriate treatment for those patients, but several issues remain after renal function restoration in a lupus recipient. This review provides insights into topics such as the frequency of lupus nephritis recurrence in the graft, the choice of immunosuppressive therapy in such cases and the management of comorbidities to reduce associated morbidities in the long term.

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INTRODUCTION

Although significant progress has been noted over the last few decades in the treatment of lupus nephritis, the incidence of end stage renal disease (ESRD) has increased significantly between 1982 and 2004; from 1.16 cases per million person-years in 1982 to 3.08 and 4.9 cases per million person-years in 1995 and 2004, respectively^[1,2]. Kidney transplantation (KTX) is the treatment of choice for patients with incident ESRD. However, current practice for those who progress to ESRD as a result of exacerbation of lupus nephritis or newly diagnosed lupus with rapidly progressive renal disease is to start with hemodialysis (HD). The rationale is to suppress any residual lupus activity, to allow the disease to become quiescent, mostly in those patients who experience a rapid decline in renal function due to aggressive lupus. Remission of lupus overall is particularly important before proceeding to transplantation, and thus, all patients with recent significant renal or extra-renal activity and ESRD begin with HD. One potential benefit from this choice is the believed "burn-out" effect of this modality on the disease^[3]. Secondly, 3 to 6 mo on dialysis, before proceed-

ing to transplantation, seem to be sufficient for renal function to recover in individuals with rapidly progressive glomerulonephritis due to lupus. In contrast, patients who are in complete remission for a considerable time period prior to ESRD, may also precede with preemptive KTX, if there is an appropriate living donor. This practice is supported by analysis of the United Network for Organ Sharing dataset from 1987 to 2009^[4], which revealed that patients with lupus nephritis who received a kidney transplant preemptively, before the need for dialysis, presented better graft survival and a lower risk of recipient death. It was associated with superior patient and graft outcomes^[4].

RENAL REPLACEMENT THERAPY FOR LUPUS PATIENTS WITH ESRD

Very few, small, retrospective studies have compared dialysis modalities to KTX in terms of cumulative survival and long-term clinical outcomes of patients. Goo *et al*^[5] studied 45 systemic lupus erythematosus (SLE) patients who initiated HD, peritoneal dialysis (PD) or KTX, between 1990 and 2000, in Korea. Disease activity, defined by the SLE Disease Activity Index, was significantly higher after PD during the 4.5 years of follow-up (HD: 5.0 ± 3.6 , PD: 7.4 ± 3.7 , KTX: 2.2 ± 1.7), whereas survival rates were similar in the three groups^[4]. Thirteen patients died during the observation period, mainly due to infections, but the type of renal replacement therapy they were under was not specified^[5]. A clear superiority of KTX, in terms of survival and complication rates, has been shown in a retrospective multicenter study by Kang *et al*^[6]. Ten-year survival in 59 individuals, who underwent KTX, PD or HD for lupus nephritis, was 90%, 81% and 55%, respectively. It should be noted however, that the transplantation group consisted of relatively younger patients. Lupus flare-up was absent among transplanted patients (0% *vs* 50% *vs* 14%) during the study period. Higher mortality rates were recorded in the HD group and they were attributed mainly to cardiovascular disease and malignancies. Only one transplanted patient died during the 10-year follow-up^[6]. Current practice in the United States population is depicted in a large analysis by Costenbader *et al*^[7], based on the United States Renal Data System. Between 1995 and 2006, 12344 patients with ESRD related to lupus nephritis were identified. Hemodialysis was the most commonly used renal replacement therapy with a significant increase during the study period (from 75.9% to 83.9%). Despite an increase in the number of living donors, KTX rates decreased markedly from 1995 to 2006, a fact that could be associated with donor organ shortage and the low socioeconomic status of several patients. Nevertheless, survival of patients undergoing KTX has shown absolutely no improvement over the 12 years of the study^[7]. Patients suffering from ESRD secondary to lupus nephritis are younger^[7,8] and severely immunocompromised due to the underlying disease and the prolonged use of immunosuppressive therapy, resulting

in several comorbidities. Thus, when planning the future of these patients in terms of renal replacement therapy, every effort should be made towards improving survival rates and quality of life.

Finally, PD is a better choice for initiating renal replacement therapy in patients with lupus and antiphospholipid syndrome, since access failure due to recurrent thrombosis is a major problem in this group of patients.

LUPUS ACTIVITY IN PATIENTS WITH ESRD

As mentioned above, from the time SLE patients progress to ESRD and start dialysis, clinical and serological activity of lupus is known to decrease. Longstanding clinical experience and research have shown that patients with renal failure resulting from lupus frequently experience a remission of their extra-renal manifestations and improvement in lupus serologic results with dialysis so that all immunosuppression can be withdrawn^[3,9,10]. Fries *et al*^[3] first described this quiescence of lupus in patients with ESRD and termed it “burnt-out lupus”. Several studies have since reported significant improvement in all autoimmune phenomena following commencement of dialysis. Mojciak *et al*^[11] found that the prevalence of patients with clinical lupus activity in the post-dialysis period diminished over time: 55%, 6.5% and 0% after 1, 5 and 10 years, respectively. They found that the serological activity in lupus was not necessarily correlated with clinical activity and that it was a more frequent condition present in 80%, 60% and 22% of the patients after 1, 5 and 10 years, respectively^[11]. Although the causes of this phenomenon are not completely understood, it is repeatedly reported and in many cases associated with gradual or partial resolution of the extra-renal manifestations of lupus^[12-14]. Less frequently, and typically in patients of black race, some investigators have reported continuation of lupus activity and occasionally exacerbation with the onset of ESRD^[15]. However, these results are better understood if we consider that they refer to varying patient populations and genetic profiles.

INCIDENCE OF RECURRENT LUPUS NEPHRITIS IN THE ALLOGRAFT

The standard concern in lupus patients who undergo KTX is lupus nephritis recurrence in the graft. Variable rates of recurrent lupus nephritis (RLN) have been reported, ranging from 0% to 44%^[16-33] with certain differences, *i.e.*, patients’ characteristics, the era of immunosuppression and the indications for renal biopsies such as protocol biopsies or serial biopsies, accounting for this. Moreover, it is essential to distinguish clinically apparent RLN in the allograft from incident histopathological findings attributable to a lupus effect in the graft without any concurrent clinical, renal or extra-renal, symptoms or signs of lupus, and thus with questionable clinical impor-

tance. The setting of RLN in transplant patients generally include renal dysfunction, either an acute increase in serum creatinine, or a slow increase compared with the baseline value, or new onset proteinuria or glomerular hematuria or both.

Clinically apparent RLN is found at an incidence rate of 2%-11%^[10,23-33]. The results from the largest cohort of patients indicate that RLN in the graft is uncommon^[28]. Specifically, 2.44% of 6850 recipients with SLE, transplanted between 1987 and 2006, developed RLN^[28]. Similarly, Stone *et al*^[33] in an earlier period, showed a rate of RLN in the graft of 2%. Burgos *et al*^[32] found an overall rate of RLN in 11% of 177 patients with SLE who underwent KTX. In our experience, RLN in the graft was documented in 7.7% of patients who underwent a graft biopsy according to clinical indication^[28]. One of these patients in our population experienced graft loss due to lupus. Moroni *et al*^[34] reported recurrence of lupus nephritis in 8.6% of the grafts, but no graft was lost because of RLN.

CLINICOPATHOLOGIC CORRELATIONS

Incidence rates of "subclinical" lupus nephritis in the allograft, *i.e.*, histopathological findings in protocol or serial biopsies, differed substantially from those which were performed solely according to clinical indication. The use of light microscopy alone, in the examination of biopsy specimens likely yielded a significantly lower rate of diagnosis of RLN. However, it was quickly recognized that transplant kidney biopsy specimens from patients with a history of ESRD as a result of lupus must additionally be evaluated by both immunofluorescence and electron microscopy. The diagnosis of lupus nephritis in the renal allograft should ideally be established after complete examination of the biopsy using the World Health Organization (WHO) or the International Society of Nephrology/Renal Pathology Society Histologic Classifications^[35], including a positive immunofluorescence microscopy, and/or the presence of electron dense deposits in the electron microscopic assessment. In this regard, when both immunofluorescence and electron microscopy were used for the evaluation of renal biopsies, along with a more aggressive protocol of graft biopsies, it was shown that 30% of the patients experienced recurrence of lupus nephritis^[26]. In the study by Goral *et al*^[26], graft survival was not influenced by recurrent disease, and the authors recommended complete morphologic study of the specimen using immunofluorescence and electron microscopy^[26]. Similarly, Nyberg *et al*^[21], in an earlier study of 16 patients with SLE, had shown that 44% had biopsy-proven RLN. Interestingly, light microscopy findings in biopsy specimens obtained from these patients were not diagnostic for RLN, but it was diagnosed by the combined use of immunofluorescence and electron microscopy^[20]. Ultrastructural evaluation with electron microscopy can be crucial in the diagnosis of patients with SLE, especially if they do not have any strong clinical manifestations and

serologic markers at the time of the kidney biopsy^[26]. Norby *et al*^[36], in a cross sectional study of lupus patients with surveillance biopsies after KTX, showed that subclinical recurrence was frequent, with 54% of the patients having RLN. The type and extent of renal involvement and activity is adequately characterized by electron microscopy in such cases^[37]. Additionally, combined evaluation with immunofluorescence and electron microscopy may play a role in distinguishing RLN from other accompanying renal abnormalities, such as acute rejection, which may also associated with mild glomerulitis^[37].

Time to RLN may also vary from days to decades after KTX. Goral *et al*^[26], demonstrated that RLN can occur as early as 6 d after transplantation. Conversely, there are reports of very late recurrence, up to 16 years post transplantation^[29]. In the same study, however, the median time to recurrence was 4.3 years post KTX^[29]. Moreover, the histopathologic lesion may be different from the one in the native kidney, and most frequently is less severe^[4,5,32]. Nevertheless, given the silent nature of many of the recurrences, it is impossible to determine the precise timing of recurrence, or the rate of recurrence in patients who did not undergo biopsies.

RISK FACTORS FOR RECURRENT LUPUS NEPHRITIS

The importance to practicing nephrologists of lupus recurrence in the renal graft is that these patients may have poorer outcomes compared with other kidney transplant recipients. However, a report of the American College of Surgeons/National Institute of Health Transplant Registry in 1975 opened the door to KTX for patients with lupus, as it was observed that they had outcomes comparable to those of non-lupus patients^[16]. Following this observation, there have been numerous studies which have found that overall 5- and 10-year graft survival rates are similar^[11,13,14,29,34,36,38-41] or comparable^[25,29] among patients with lupus and those with other primary diseases. Recognized risk factors for allograft loss in lupus patients include black non-Hispanic ancestry, female gender, and young age^[29,32]. Patients with antiphospholipid autoantibodies^[34] and those receiving the kidney from living donors^[36] also have a higher risk of recurrence. African American ethnicity was shown to be independently associated with RLN in the allograft and possibly with diminished survival^[32]. Dooley *et al*^[42] had earlier shown that, compared with Caucasians, lupus nephritis developed more frequently in African Americans (60% *vs* 25%). Furthermore, African Americans displayed a less favorable response to treatment and thus the disease progressed to ESRD at a higher rate^[42]. Consistent with this, Contreras *et al*^[29] found that black non-Hispanic and female recipients had, respectively, 1.88- and 1.70-fold increased risk for the development of RLN. The same study demonstrated that recipients younger than 33 years had a 1.69-fold increased risk for the development

of RLN. Onset of SLE and ESRD at a younger age in a black woman usually predicts a more aggressive disease^[29]. Recurrent lupus nephritis and chronic rejection of the kidney were shown to be risk factors for allograft loss (HR = 2.48; 95%CI: 1.09-5.60 and HR = 2.72; 95%CI: 1.55-4.78, respectively) in the study by Burgos *et al.*^[32]. However, Stone *et al.*^[33] had found that RLN did not invariably result in allograft failure. The same study demonstrated that short time period of pre-transplantation dialysis, *i.e.*, less than 6 mo, had no adverse effect on KTX outcome in 10 of 11 studies that examined the relationship^[33].

DIAGNOSIS AND TREATMENT OF RLN IN THE ALLOGRAFT

RLN in the allograft should be suspected in any patient who progresses to ESRD due to renal lupus, in the light of certain clinical and/or laboratory findings. Thus, new onset proteinuria or glomerular hematuria should directly lead to the suspicion of lupus nephritis in the allograft. However, rapid worsening of previously existing proteinuria should also raise the suspicion for RLN, especially with the coexistence of glomerular hematuria. The clinical presentation of increased serum creatinine is also typical of patients with RLN in the graft. However, among all transplant recipients who present with an elevated serum creatinine, there are certain other parameters that need to be excluded as possible contributors before considering a diagnosis of RLN. These include dehydration, toxic concentrations of serum calcineurin inhibitors, and obstructive uropathy. Diagnosis of RLN is made by biopsy and histopathologic evaluation by light microscopy, immunofluorescence and electron microscopy as discussed earlier. Measurement of serologic parameters, such as complement levels and titers of anti-double stranded DNA antibodies is not helpful in establishing the diagnosis in the allograft^[24,33].

Immunosuppressive therapy

Kidney transplant recipients with recurrent lupus usually do not require any change in the immunosuppressive regimen, as they already receive maintenance therapy for the transplant. Most are shown to have mild lesions in the graft due to lupus, as demonstrated by surveillance biopsy studies^[36]. Specifically, most of the patients had subclinical disease of class I or II in the biopsy^[36]. On the other hand, the vast majority of patients had chronic allograft nephropathy (84%)^[43], while they were also susceptible to calcineurin inhibitor toxicity, as are SLE patients who have not had transplants^[42]. Besides, the major impediment to the goal of improved kidney transplant survival is a cumulative and progressive immune and non-immune injury^[43,44]. In kidney transplant recipients with SLE, standard immunosuppression with a calcineurin inhibitor, mycophenolate mofetil and prednisone seems to protect against clinically overt recurrent disease, but not against chronic allograft nephropathy^[36]. Importantly, indices of

lupus activity were found to be low in the study by Norby *et al.*^[36], and did not differentiate between patients with RLN and those without recurrence.

However, there are select patients who require additional immunosuppressive treatment. In terms of renal involvement, these mostly include patients with clinically evident disease and severe histopathologic lesions, consistent with WHO class III or IV^[35] in the graft. Among patients who have a histologic diagnosis of recurrent lupus in the graft, along with rapid deterioration of renal function, all other factors associated with acute renal dysfunction in a kidney transplant recipient should be excluded at first, *i.e.*, acute rejection, chronic allograft nephropathy, calcineurin inhibitor toxicity. Following this workup, any lupus patient with new onset proteinuria or worsening proteinuria and/or hematuria in the presence of severe proliferative lesions in the graft biopsy requires the existing immunosuppressive regimen to be modified. Depending on the clinical picture and morphologic lesions, we use either higher doses of mycophenolate mofetil or (2-3 g/d), or initiate cyclophosphamide intravenously along with discontinuation of the current antimetabolite. Both of these options are always accompanied by glucocorticoids, usually pulses of methylprednisolone, 500-1000 mg/d for 3 consecutive days, which are followed by a tapering steroid regimen. We tend to choose cyclophosphamide in cases who present with rapid renal deterioration combined with a crescentic pattern in histology, and in all cases with severe extra renal disease, *i.e.*, pulmonary hemorrhage, central nervous system involvement, or any other life-threatening phenomenon attributable to lupus. Although there is not sufficient data to support the use of the aforementioned agents in the lupus transplant recipient with recurrence, this approach is based upon studies of patients with lupus nephritis involving the native kidney^[45]. Similarly, the optimal scheme of cyclophosphamide for these patients, who already carry a considerable load of immunosuppression starting from their initial diagnosis of SLE, is not known. One reasonable option is the Euro lupus regimen, which consists of 6 intravenous pulses of 0.5 g cyclophosphamide^[46]. Patients of black ethnicity may need more aggressive therapy, with monthly courses of cyclophosphamide of 0.5-1 g/m² body surface area. In any case, the leukocyte nadir is the main guide of therapy, *i.e.*, less than 4000/ μ L and absolute neutrophil count less than 1500/ μ L. However, the maximum dose of cyclophosphamide should not exceed 1 g/m² body surface area.

In cases of resistant RLN despite the use of mycophenolate mofetil and cyclophosphamide, the only treatment option is rituximab along with an increase in glucocorticoids. Nevertheless, there are no published data to support the use of rituximab in RLN among kidney transplant recipients, but only a few observational studies and case reports of the successful use of rituximab in patients who suffer from lupus nephritis in the native kidney and are resistant to mycophenolate mofetil and cyclophosphamide^[45,47-49]. As the optimal scheme is not

known, one may use the same dose as for lupus nephritis in the native kidney, *i.e.*, 1 g given on days 1 and 15, or 375 mg/m² body surface area as given in antineutrophil cytoplasmic autoantibodies glomerulonephritis^[50,51]. Yet, even with data on a considerable number of patients treated with rituximab, we should always keep in mind that the long-term toxicity has not been completely defined in the transplant population^[51].

Non-immunosuppressive therapy

We treat all patients with histopathologic changes of RLN in the graft and protein excretion, typically more than 0.5 g/d with renin angiotensin system blockade. The notion for this approach is based upon studies in non-transplant patients with chronic kidney disease and proteinuria, where it has been shown that renin angiotensin system blockade decreases the progression of renal disease^[52]. Anemia and hyperkalemia may be seen with the angiotensin converting enzymes inhibitors, but this issue is usually circumvented by the fact that transplant recipients are generally closely followed and such side effects are readily detected. Moreover, the long-term benefit from renin angiotensin system blockade outweighs the risk of experiencing such events.

MANAGEMENT OF COMORBIDITIES

Death with a functioning graft is a major cause of renal allograft loss in the general population. The same applies to recipients with ESRD due to lupus nephritis, and is mainly attributed to cardiovascular disease^[53].

Cardiovascular disease

Although SLE predominantly affects young females of childbearing age, studies point out that the disease is characterized by an accelerated atherosclerotic mechanism, which increases cardiovascular morbidity and mortality^[53,54]. Furthermore, the study by Costenbader *et al.*^[7], recorded an increased trend towards cardiovascular risk factors, namely smoking, obesity, diabetes mellitus and hypertension in incident SLE-related ESRD patients, in the years 1995-2006. Several small, mostly retrospective, single-center studies with limited numbers of patients indicate cardiovascular disease as the leading cause of morbidity and mortality in transplanted patients secondary to lupus nephritis^[28,47,55]. A retrospective analysis of data from the United States Renal Data System and the United Network for Organ Sharing was conducted between 1990 and 1999. Among 2886 patients with lupus nephritis undergoing a renal transplant, cardiac events and cerebrovascular disease were the main causes of death. However, non-SLE recipients (*n* = 89958) exhibited a higher rate of these comorbidities, probably because they were older, with a higher prevalence of pre-existing cardiovascular disease and diabetes mellitus^[55]. According to data from the National Transplant Center in Norway, 77 patients with SLE underwent first and subsequent KTX from 1972 to 2005. They were compared with 154

matched non-SLE transplanted patients. Norby *et al.*^[56] also found that the main cause of death was cardiovascular disease, with acute myocardial infarction as the major factor. Notably, death from cardiac-associated events occurred much earlier in SLE patients compared to the control group (median time: 3.9 years *vs* 13.0 years).

No specific data exist to date comparing morbidity between deceased and living donor KTX in this patient population, although living donation in these patients has been associated with improved patient and graft survival^[44].

Other comorbid conditions

An area of major concern has always been a previous history of antiphospholipid antibody syndrome (APAS), or solely the presence of these antibodies in this patient population, because of the risk of graft or other vascular thrombosis. Vaidya *et al.*^[57], recently showed that the 10-year renal allograft survival is significantly lower among patients with APAS, compared with those who have only circulating antibodies. Careful monitoring is mandatory in order to avoid thrombotic episodes.

Infections (sepsis, pneumonia, viral infections, fungal infections, tuberculosis, urinary tract infections) have been reported as causes of morbidity and mortality after KTX due to lupus nephritis^[6,28,47,53-55]. One could hypothesize that prolonged exposure to immunosuppressive agents prior to ESRD, as well after ESRD and KTX predisposes to infections. However, published data are contradictory as the prevalence of serious infections is not always higher in SLE recipients compared with non-SLE patients^[6,57].

Malignancies, orthopedic complications, such as avascular necrosis of the femur head and osteoporosis have been rarely reported in various studies as late complications in kidney transplant SLE recipients^[6,47].

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