REVIEW

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Lupus nephritis and kidney transplantation: past, present and future

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ABSTRACT

Background: Systemic lupus erythematosus (SLE), an autoimmune inflammatory disease that affects various organ systems, has a severe form called lupus nephritis (LN). The management of LN has changed over the past few decades due to the discovery of new immunosuppressive drugs and advances in our understanding of the disease process. This study evaluates lupus nephritis and kidney transplantation in the past, present, and future challenges.

Methods: This literature review compiles and elaborates on previous studies from many authors to support future experimental studies, which will be conducted to evaluate the challenges of lupus nephritis and kidney transplantation management according to past, present, and future data.

Results: Treatment strategies for LN typically involve a combination of immunosuppressive medications, such as corticosteroids, cyclophosphamide, and mycophenolate mofetil, to induce and maintain remission. Many LN patients progress to ESRD, necessitating renal replacement therapy (RRT) through dialysis or kidney transplantation. The results of kidney transplantation in LN patients have been progressively improving. Developing novel immunosuppressive agents may improve graft survival and reduce complications in LN patients undergoing kidney transplantation.

Conclusion: The future of kidney transplantation for LN patients appears promising, with emerging research focused on novel immunosuppressive agents, personalized medicine, biomarkers for predicting recurrence and graft rejection, preventive strategies for recurrent LN, and cell-based therapies

Keywords: Lupus Nephritis, Kidney Transplantation, Immunosuppressive agent.
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INTRODUCTION

Systemic lupus erythematosus (SLE), an autoimmune inflammatory disease that affects various organ systems, has a severe form called lupus nephritis (LN).[1] According to The American College of Rheumatology (ACR) criteria, lupus nephritis manifests both clinical and laboratory manifestations (persistent proteinuria >0,5 g per day or more significant than 3+ by dipstick and/or cellular casts including red cell hemoglobin, granular, and tubular or mixed.[2] LN is characterized by inflammation and damage to the glomeruli, the kidney's filtering units, which can ultimately lead to kidney failure and end-stage renal disease (ESRD).[3] Up to 60% of adult patients with SLE suffer from LN, significantly contributing to high morbidity and mortality in this population.[4]

The diagnosis of LN examined active urine sediment, worsening proteinuria, and decreased renal function. In some complicated cases, it may be challenging to recognize whether there was a sign of SLE activity or non-immunological causes. An invasive procedure such as a renal biopsy can be performed in complex cases, but this procedure has complications. Immunologic biomarkers can measure the severity of disease activity.[5]

A retrospective review of 105 patients with LN from 1995 to 2007 evaluated the prognosis of clinical, histological, and immunological characteristics. Several factors are associated with poor renal outcomes in LN patients, such as hypertension, elevated serum creatinine, and black subjects, as they are related to low socioeconomic status and genetics. The prognosis of 5 and 10-year survival rates were 54% and 41%. This poor outcome can be caused due to late diagnosis of SLE, persistent proteinuria at diagnosis of SLE, delay in diagnosis of LN, and inadequate skill of health personnel. Sepsis and renal failure account for 70% of deaths. Patients with SLE are immunocompromised due to long-term immunosuppression therapy.[6]

Following the identification of the proliferative histologic subtype, the management of LN has changed over the past few decades due to the discovery of new immunosuppressive drugs and advances in our understanding of the disease process.[7] Treatment strategies for LN typically involve a combination of immunosuppressive medications, such as corticosteroids, cyclophosphamide, and mycophenolate mofetil, to induce and maintain remission.[2] Despite these advancements, a significant proportion of LN patients progress to ESRD,

necessitating renal replacement therapy (RRT) in the form of dialysis or kidney transplantation.[8]

Since kidney transplantation offers a greater quality of life and survival rate than long-term dialysis, it has been recommended as therapy for ESRD in SLE patients.[9] The results of kidney transplantation in LN patients have been progressively improving, with graft survival rates that are equivalent to those of patients with ESRD from other causes.[10] This development can be due to improvements in surgical procedures, post-transplant care, and immunosuppressive treatments.[11]

However, LN patients face unique challenges in the context of kidney transplantation, such as the risk of recurrent disease, increased susceptibility to infection, and potential complications related to their underlying autoimmune condition.[12] As a result, there is a continuous need for research to improve transplant outcomes and address the unmet needs of this patient population.

Based on those mentioned above, this article provides an overview of kidney transplantation's past, present, and potential future outcomes for LN patients. This literature review will analyze the evolution of immunosuppressive therapies and their impact on graft survival, explores the challenges faced by LN patients undergoing transplantation, and highlights novel treatments and potential future directions in the field.

THE PAST: THE EVOLUTION OF KIDNEY TRANSPLANTATION IN LUPUS NEPHRITIS

Early Days of Transplantation and Immunosuppression

In Boston, Massachusetts, identical twins received the first successful kidney transplant. Dr. Thomas Earl Starzl demonstrated in 1963 that organ rejection might be avoided by swiftly adding corticosteroids to azathioprine. However, in the years following Hans Peter Frey's 1969 discovery of cyclosporine and its subsequent 1979 introduction into clinical practice, the results of kidney transplantation considerably improved. One of the first doctors who used cyclosporine in human transplantation was Dr. Starzl, also one of the pioneers of using Tacrolimus. This discovery has led to a further expansion of indications for kidney transplantation and an improvement in the results, particularly in the short term. Because of his research and expertise, Dr. Starzl is known as the "*Father of Transplantation*".[13] However, it wasn't until the development of immunosuppressive therapies, such as corticosteroids, azathioprine, and cyclophosphamide, that transplantation became more widely accepted for treating LN-induced ESRD. Using these agents allowed for better control of the recipient's immune response, reducing the risk of graft rejection and improving patient outcomes.[14]

Advancements in Immunosuppression and Graft Survival

The introduction of calcineurin inhibitors (CNIs), like cyclosporine and tacrolimus, in the 1980s significantly improved graft survival rates.[13] Tacrolimus is a common immunosuppressant in solid organ transplantation. CNIs constituted a breakthrough in transplantation by enabling stronger and more focused immunosuppression.[15] Mycophenolate Mofetil (MMF) also became a vital part of the accepted standard of treatment for kidney transplantation as it proved to be a potent immunosuppressant for preventing acute rejection.[16]

Evolution of Transplantation Protocols and Patient Selection

Over the years, transplantation protocols have evolved to serve LN patients better. A vital aspect of this evolution has been the development of criteria to determine the optimal timing of the transplantation and the selection of suitable candidates. These criteria typically include assessing disease activity, ensuring adequate immunosuppression, and evaluating the patient's health.[17] Due to technological advancements, sensitive tests to identify anti-HLA at donor-specific antibodies (DSAs) have been developed. These tests include flow cytometry cross-match and solid-phase assays (SPAs), including Luminex. Systematic review and meta-analysis examined seven retrospective studies comparing positive and negative DSA-PSA in the presence of negative CDC. Negative flow cross-match revealed a considerably higher probability of biopsy-confirmed AMR and allograft failure in the DSA-SPA-positive group.[17]

Improved Understanding of LN Pathogenesis and Treatment

The 2010s witnessed significant advancements in understanding LN pathogenesis, leading to new treatment strategies to manage the disease and reduce the risk of progression to ESRD.[1] This period saw the introduction of newer immunosuppressive agents, such as belimumab, which showed promising results in managing LN.[18] Furthermore, research into the role of genetic and environmental factors in LN has provided valuable insights into the disease process and potential targets for therapy.[3]

PRESENT: CURRENT STATE OF KIDNEY TRANSPLANTATION IN LUPUS NEPHRITIS

Modern Immunosuppressive Regimens and Graft Survival

The use of immunosuppressive drugs is developing quickly. Mycophenolate mofetil was recommended as an alternate drug for induction and maintenance therapy in lupus nephritis because it had less gonad toxicity than standard immunosuppressive medications (cyclophosphamide and azathioprine), which have inadequate efficacy and significant toxicity. In crucial research, it did not demonstrate superiority over cyclophosphamide.[19]

Modern immunosuppressive regimens, which typically include a combination of corticosteroids, calcineurin inhibitors (CNIs), and mycophenolate mofetil (MMF), have led to significant improvements in graft survival rates for LN patients undergoing kidney transplantation.[4] Research has also focused on identifying the optimal immunosuppressive regimen for LN patients, considering factors such as the patient's risk of rejection, infection, and malignancy.[7]

A study by Lionaki et al. compared the outcomes of kidney transplantation

in patients with LN and other causes of ESRD.[20] The authors found that LN patients had similar graft survival rates as patients with different etiologies, demonstrating the effectiveness of modern immunosuppressive regimens in this population.[7]

Addressing Recurrent Lupus Nephritis in the Transplanted Kidney

One of the significant challenges faced by LN patients undergoing kidney transplantation is the risk of recurrent disease in the transplanted kidney. Studies have shown that recurrence rates can range from 10-30% and recurrent LN is associated with worse graft outcomes. The median duration for recipients to develop recurrent LN after transplantation was 1561 days (with a range of 1 to 5594 days), according to a cohort analysis of 6850 recipients of kidney allografts with systemic lupus erythematosus (Figure 1).[9] Recurrent Lupus Nephritis in allograft should be suspected in any patient who progresses to ESRD due to renal lupus. Recent research has aimed at identifying risk factors for recurrence and developing targeted therapies to prevent or treat recurrent LN.[11]

A retrospective cohort study of LN patients following kidney transplant found that anti-double-stranded DNA antibodies, low blood C3 levels, and a high SLE disease activity index score were all related to an elevated risk of recurrent LN.[6] Increased creatinine, glomerular hematuria, and proteinuria of recent beginning may be signs of lupus nephritis in the allograft. Before making the diagnosis of recurrent lupus nephritis, other factors must be taken into account as potential causes. This involves obstructive uropathy, hazardous levels of serum calcineurin inhibitors, and dehydration. The results of a biopsy and histopathologic examination using light, immunofluorescence, and electron microscopy are used to make the diagnosis of recurrent lupus nephritis.[20]

Comparative studies and case series found that patients with absent or low lupus activity for at least 3-6 months are good candidates for kidney transplantation. Patients with moderate to high titers of antiphospholipid antibodies are at increased risk for thrombotic complications.[7] These findings suggest that the careful monitoring of such risk factors may help to guide post-transplant management in LN patients.

Management of Comorbidities and Post-Transplant Complications

LN patients often face additional challenges in the post-transplant setting due to comorbidities, such as cardiovascular disease, infection, and malignancy, impacting graft survival and patient outcomes.[12] Thus, a multidisciplinary approach to care, including close monitoring and managing comorbidities, is critical for optimizing patient outcomes in this population.[10]

A recent study by Pattanaik et al., evaluated the impact of comorbidities on graft survival in LN patients undergoing kidney transplantation.[21] The authors found that comorbidities were associated with a higher risk of graft failure, emphasizing the importance of comprehensive management of these conditions in the post-transplant period.[21]

Both prospective and retrospective investigations have found significant variations in the incidence and clinical effects of recurrent lupus nephritis (RLN) among kidney allograft patients with systemic lupus erythematosus (SLE). Patients in the RLN group frequently got kidney allografts from decreased donors with a high level of LA-A and HLA-B locus mismatch, increased frequency of zero-haplotype match with their living donors, and elevated panel-reactive antibodies.[9]

Living Donor Kidney Transplantation in LN Patients

Living donor kidney transplantation has been increasingly recognized as a valuable option for LN patients, offering reduced waiting times compared to deceased donor transplantation. A previous study found that deceased-donor transplants had a higher adjusted mortality hazard ratio of 0.32 (95%CI, 0.29-0.36) than living-donor transplants for 0.24 (95%CI, 0.21-0.27).[22] Another study also showed that living donor kidney transplantation had a better 1- and 5-year patient survival, for 93% and 83.3%, respectively. Meanwhile, in the deceased donor kidney transplantation, the 1- and 5-year patient survival was 79.1% and 74.5%.[23] These findings highlight the potential benefits of living donor transplantation for LN patients.

THE FUTURE: EMERGING TREATMENTS AND RESEARCH DIRECTIONS IN KIDNEY TRANSPLANTATION FOR LUPUS NEPHRITIS

Novel Immunosuppressive Agents and Personalized Medicine

Developing novel immunosuppressive agents may improve graft survival and reduce complications in LN patients undergoing kidney transplantation. Investigational agents, such as belatacept, a costimulation blocker, and voclosporin, a novel calcineurin inhibitor, have shown promise in improving transplant

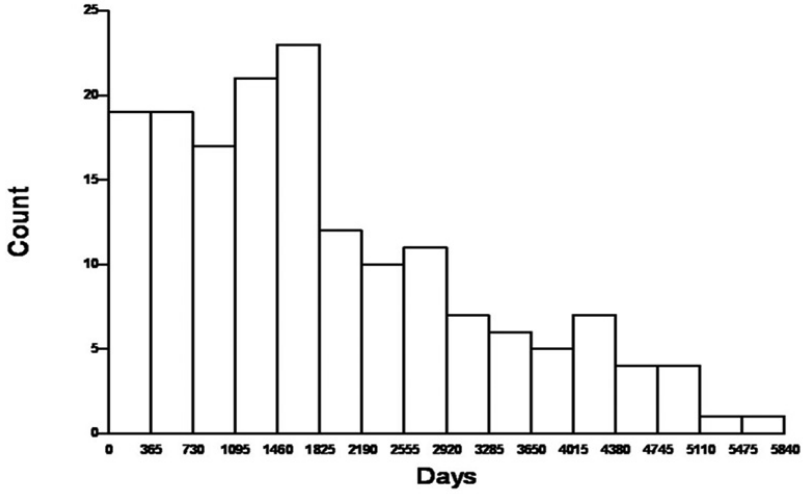

Figure 1. Duration of Recurrent Lupus Nephritis After Kidney Transplantation.[9]

outcomes and potentially reducing side effects associated with current immunosuppressive regimens.[24,25] A previous phase 3 RCT study about belatacept-based immunosuppression, both the more intensive and the less intensive regimen, compared with the cyclosporine regimen, showed a 43% reduction in the risk of death or graft loss. Across the 7-year observation period, the mean estimated glomerular filtration rate (eGFR) increased with both belatacept regimens but decreased with the cyclosporine regimen (P<0.001 for the overall treatment effect of each belatacept regimen vs. cyclosporine) (**Figure 2**).[24]

Another RCT study about a novel immunosuppressive agent, voclosporin, has been done in 20 countries. This research found that combining low-dose voclosporin with mycophenolate mofetil (MMF) and corticosteroids for induction treatment of active LN leads to a better renal response than MMF and corticosteroids alone but at a higher risk of side effects was observed. This trial included a multi-ethnic global population, indicating that calcineurin inhibitor-based therapy may be suitable for all patients with LN.[25] The implementation of personalized medicine strategies, including pharmacogenomics and tailored immunosuppression, may help to optimize individual patient outcomes by accounting for genetic variability and specific risk factors.[26]

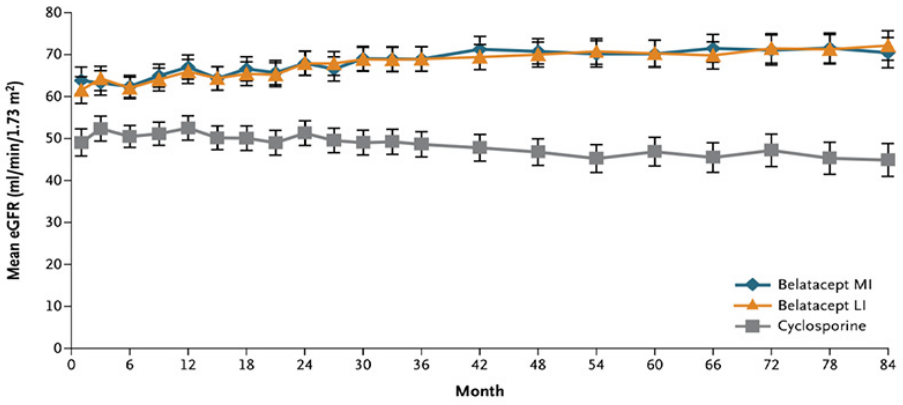

Figure 2. Glomerular Filtration Rate in Patients with Immunosuppression Agents

Biomarkers for Predicting Recurrence and Graft Rejection

Identifying reliable biomarkers for predicting recurrent LN and graft rejection is an active research area, as these factors can significantly impact graft survival and patient outcomes. Recent studies have suggested that certain serum and urinary biomarkers, such as anti-C1q antibodies and urinary monocyte chemoattractant protein-1 (MCP-1), may hold promise in predicting LN recurrence and graft rejection.[5,27] The previous study showed that anti-C1q antibodies have a sensitivity of 80.5% and a specificity of 71% for diagnosing flares in LN patients. It also has a high negative predictive value of 94% but a poor positive predictive value of 38%. Through multivariate analysis, the best model for predicting renal flares was achieved by combining anti-C1q antibodies with C3 and C4.[5]

Another preferable biomarker can be tested repeatedly in noninvasively obtained samples. Urine biomarkers are appropriate for immunological surveillance after kidney transplantation because it is produced directly by the allograft and can be continually collected for testing. After kidney transplantation, proinflammatory cytokines are released from allografts, stimulating the local secretion of chemokines.[28,29] Urinary MCP-1 one week after kidney transplantation (KT) might be considered for predicting early acute rejection with a sensitivity of 84.6% and specificity of 64.8%.[30] Another potential biomarker one week after KT for predicting early acute rejection was urinary fractalkine, with a sensitivity of 61.5% and specificity of 77,8%. Besides that, protocol biopsy revealed a positive correlation between intrarenal T cells and B cells.[30] The tubular epithelium and endothelium of the allografts in acute rejection patients showed significantly increased levels of fractalkine expression.[31]

Another long-term biomarker that can be used to predict treatment response at 6 months is the urinary Epidermal Growth Factor (EGF). It had a sensitivity of 85% and specificity of 71% for EGF ≥ 65.6 ng/mgCr. As glomeruli and tubules express EGF protein and mRNA, most EGF is produced locally in the kidney.[32,33] The epidermal growth factor receptor is a site of autocrine and paracrine signaling that supports cell survival, differentiation, and proliferation.[34] High proteinuria did not increase the EGF limitation, although it did connect with GFR and the chronicity index. The urine MCP-1 marker, however, indicates increased lupus nephritis activity.[35] Further validation of these biomarkers in large-scale, prospective studies is needed to establish their clinical utility in managing LN patients undergoing kidney transplantation.

Preventive Strategies for Recurrent Lupus Nephritis

Another area of ongoing research is the development of preventive strategies to reduce the risk of recurrent LN in the transplanted kidney. Recent studies have explored using B cell-targeted therapies, such as Rituximab, as a potential prophylactic approach to prevent LN recurrence.[36] Rituximab (RTX) had a total remission (TR) rate of 81.9% (95% CI, 73.7-88.8%) and a complete remission (CR) rate of 46.6% (95% CI, 36.4%-57.2%) in 28 case series according to a prior meta-analysis study. In 2021, Shen L et al., A chimeric monoclonal antibody called rituximab specifically targeted the CD20 antigen on the surface of B cells and directly or indirectly eradicated pathogenic B lymphocytes.[16,37] Rituximab treatment controlled B lymphocyte malfunction and lowered the amount of self-reactive memory B cells.[38] Rituximab and tacrolimus were also found to be the most effective medications for providing lupus nephritis patients into remission in another meta-analysis study. Tacrolimus is the least harmful medication and has the lowest risk of infection-related side effects.[16] This meta-analysis study is in accordance with another study that showed the most effective induction therapy and the least risk of serious infection was

Tacrolimus.[39] Another potential preventive of LN was Mycophenolate Mofetil (MMF) which had a better complete remission than Cyclophosphamide (CYC) (OR = 1.60; 95% CI, 1.00-3.20).[39] Furthermore, a better understanding of the mechanisms underlying LN recurrence may help guide the development of targeted therapies and preventive strategies.

Cell-Based Therapies

Cell-based therapies, including mesenchymal stem cells (MSCs) and regulatory T cells (Treg s), have emerged as promising treatment modalities for autoimmune diseases, including SLE and LN.[41,40] Non-hematopoietic multipotent progenitor cells known as MSCs have the ability to differentiate into a variety of cell types, including osteoblasts, chondrocytes, myoblasts, adipocytes, and hepatocytes. MSCs, which are simple to separate, grow and have a great capacity for proliferation, mediate immunological responses. According to preliminary research by Liang J et al., MSC transplantation can improve lupus nephritis in animal models.[41] Cell-based therapies may have potential benefits in preventing and treating LN recurrence in the transplanted kidney, even if human clinical trials are still in the early phases of development.[41] Hypothesized SLE is potentially an MSC-mediated disease. Allogenic transplantation will give better outcomes than autologous bone marrow-derived MSCs transplantation. Compared MSCs from a patient with lupus and controls showed decreasing cytokines (TGF-β), Interleukin 6 (IL-6), and IL-7 mRNA. Fifteen patients with SLE refractory treated with allogenic MSCT trial showed decreased ANA and anti-dsDNA after MSCT and reduced 24h proteinuria. About 73% of patients had a significant reduction in fatigue, weight loss, and low-grade fever. There are no serious adverse events reported in this journal. The most common adverse event was upper respiratory tract infection. The mechanism by which allogeneic MSCT improves lupus remains a matter of debate. There are several hypotheses about MSCT. MSCs work as immunomodulators by producing soluble factors. MSCT is associated with the expansion of Tregs, which can inhibit autoreactive T cell activity and are related to self-tolerance maintenance. Human BM-MSCs can differentiate into endothelial cells in vitro.[41-44]

The management of lupus nephritis (LN) and kidney transplantation has significantly improved over the past several decades. In the past, a limited understanding of the disease and its complications and rudimentary immunosuppressive regimens led to suboptimal outcomes for LN patients undergoing kidney transplantation. Recent advances in surgical methods, immunosuppressive treatments, and a better comprehension of LN pathophysiology have markedly improved graft survival rates and patient outcomes.

The implementation of modern immunosuppressive regimens marks the present state of kidney transplantation for LN patients, advances in the identification and management of comorbidities, and increased utilization of living donor kidney transplantation. These developments have led to comparable graft survival rates for LN patients compared to patients with other causes of end-stage renal disease.

The limitation of this study is the lack of information and research on lupus nephritis treatment in developmental countries. Better data collection regarding therapy and treatment success is needed to develop new therapies. A survival analysis study of mortality and the onset of lupus nephritis in patients with systemic lupus erythematosus is required to track the effective treatment for LN patients.

CONCLUSION

The future of kidney transplantation for LN patients appears promising, with emerging research focused on novel immunosuppressive agents, personalized medicine, biomarkers for predicting recurrence and graft rejection, preventive strategies for recurrent LN, and cell-based therapies. As our understanding of LN pathogenesis and treatment continues to evolve, further advancements in kidney transplantation for LN patients are expected to lead to even better outcomes and quality of life for these individuals. A comprehensive, multidisciplinary approach to care, incorporating past, present, and future advancements, will be essential for optimizing patient outcomes in LN kidney transplantation.

CONFLICT OF INTEREST

There is no conflict of interest for this manuscript.

ETHICAL CONSIDERATION

Not applicable.

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AUTHOR CONTRIBUTION

All authors have contributed to this research process, including conception, design, collection and assembly of data, analysis and interpretation of the data, drafting of the article, and critical revision of this manuscript.

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