Renal transplantation in lupus nephritis

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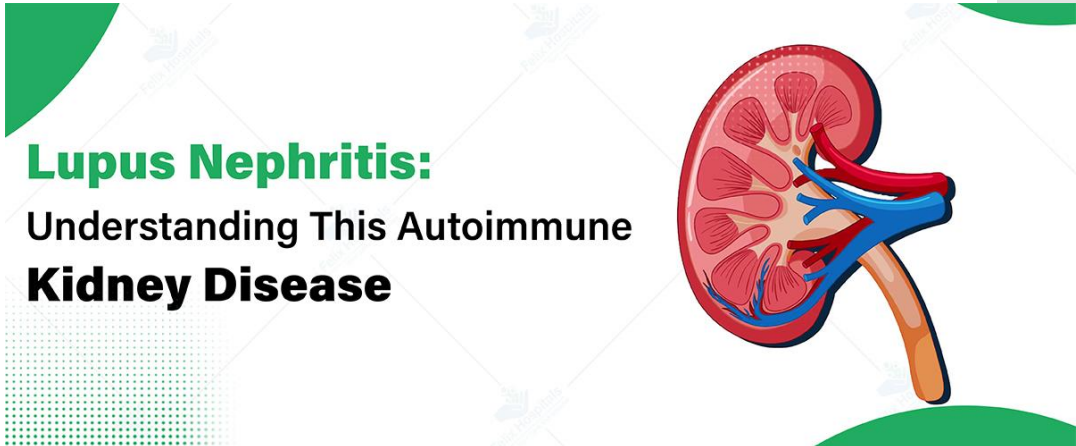
- Lupus nephritis (LN) is an important cause of morbidity and mortality due to the possibility of progression to renal failure and/or treatment-related complications

- Approximately 50-60% of patients with SLE develop lupus nephritis (LN) within the first ten years of diagnosis



- 5-year survival rate is significantly lower for SLE patients with than without LN

- 10–30% of SLE patients with LN develop end-stage chronic kidney disease (CKD) within 15 years of LN diagnosis, despite aggressive treatment
- five-year risk for developing end stage renal disease (ESRD) is 10-70% among lupus nephritis patients

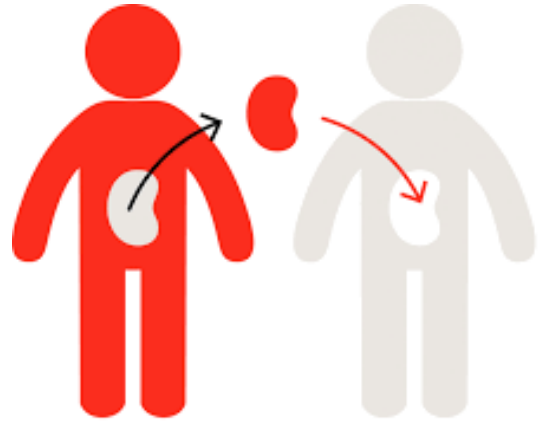
- depending upon the severity of the disease,
- Specifically:
- younger age (< 33 years)
- non-European ancestry
- Male gender (in some but not all series)
- Abnormal serologic tests
- Disease activity

- were found to associate with earlier development of renal disease.

OUTCOMES AFTER TRANSPLANTATION

- Renal transplantation is a viable treatment option for patients with end-stage CKD and LN
- Renal transplantation is **superior** to dialysis in improving quality of life, survival, and complications

- **The reported 10-year patient survival in the literature varies between 60% and 86%**



- In an analysis of 20,974 patients diagnosed with ESKD due to LN, kidney transplantation, compared with no transplantation, was associated with a 70 percent reduction in all-cause mortality

- risk of graft failure is similar in renal transplantation patients with and without SLE
- Relapse of LN in the allograft increases the risk of graft failure, but the occurrence of graft loss is rare
- rates of LN-related complications and recurrence are low

- mean duration of hospitalization after kidney transplantation was significantly higher in the SLE patients

Timing and type of transplantation

- In the past,
- period of quiescent clinical and serologic activity was required before transplantation in patients with SLE and ESKD.
- Some advised dialyzing patients for at least three to six months and up to one to two years to allow their disease activity to "burn out"

- Particular attention should be paid to the disease activity and its treatment.
- Usually the activity of lupus quenches when uremia develops, frequently allowing complete cessation of steroid treatment after dialysis is started.
- Some patients may show frequent flares of SLE during dialysis and require an aggresive treatment with corticosteroid and immunosuppressive agents

- no evidence-based guidelines on how long a patient who has ESKD due to lupus nephritis (LN) should wait prior to kidney transplantation.
- suggest not setting an arbitrary waiting time on dialysis before transplantation for most patients with SLE.

ORIGINAL ARTICLE

Impact of pre-transplant time on dialysis on survival in patients with lupus nephritis

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- For every additional month on dialysis, prognosis worsened by 1.3%.

- If patients exceeded a binary cut-off of 24 months on dialysis in our cohort, there was a suggestion that this conferred almost a three fold increase in mortality

- presence of serologic disease activity at the time of transplantation has not been shown to correlate with transplant outcome.

- A systematic literature review and analysis of the Toronto lupus cohort found that the persistence of serologic abnormalities at the time of transplantation was not associated with graft failure

- for patients with rapid progression to renal failure suggest:

- waiting at least three months before transplantation, in order to evaluate a possible recovery of renal function

- With the exception of these cases,

- patients should receive renal transplantation **as soon as possible**,

- Patients who have a potential living donor should undergo preemptive transplantation provided their extrarenal manifestations of SLE, if present

Risk factors for renal transplant :

- Black non-Hispanic had 1.88--fold increased odds for the development of RLN (the strongest predictor of the development of RLN)
- female recipients and 1.70-fold increased odds for the development of RLN
- recipients who were younger than 33 years had 1.69-fold increased odds for development of RLN.

Types Donor:

- living-donor transplantation might be the preferred treatment option

- significantly lower 5-year graft survival for cyclosporine treated recipients of cadaveric grafts than for controls and cyclosporine-treated living allograft recipients

Types of dialysis :

- may also influence the results of transplantation
- results being particularly poor in patients treated with peritoneal dialysis

Presence of antiphospholipid antibodies

- Antiphospholipid antibodies (aPL) are detected in up to 40 percent of patients with SLE
- development of antiphospholipid syndrome (APS) is much less common.
- patients with SLE who also have aPL are at increased risk for thrombotic events, including the development of thrombotic microangiopathy in the allograft

- All patients should be tested for the presence of aPL prior to transplantation.

- Patients who develop APS should be treated with anticoagulation

- Some centers routinely start all such patients on low-dose aspirin (81 mg daily).

- In addition,
- use of oral vitamin K antagonists prevents allograft thrombosis in patients who are aPL positive
- benefits of anticoagulation must be weighed against the risks of bleeding, and therapy should be individualized

- It is unclear if the use of sirolimus provides added benefit against recurrent coagulation or graft loss in this lupus population

Immunosupprive therapy for antirejection

- Induction and maintenance immunosuppressive regimens to prevent rejection are the same among patients with ESKD from LN as among patients with other forms of kidney disease,

- use of glucocorticoid-free regimens among patients with ESKD due to LN is not standard practice.

- effect of immunosuppression on the recurrence of lupus nephritis in the graft kidney varies among studies.

- recurrence rate was higher (3.9% vs. 1.98%) among patients who were transplanted before January 1996 versus patients transplanted after January 1996

- Overall graft survival rates in these studies is higher for patients being treated with cyclosporine than for those on azathioprine

- Azathioprine was associated with a higher rate of recurrence
- **but both tacrolimus and MMF have favorable effects on relapse**
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- MMF was associated with better graft and patient survival

LUPUS SCIENCE & MEDICINE™

Belatacept in kidney transplant patients with systemic lupus erythematosus

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ABSTRACT

Objectives Lupus nephritis (LN) requires renal replacement therapy in 10%–30% of patients. About 30% of these patients receive a kidney transplant. Belatacept

within 15 years of diagnosis,[3] and about 30% eventually become kidney transplant recipients.[4] LN decreases life expectancy by 15.1 years compared with patients without renal

Belatacept in LN kidney transplant recipients

Belatacept is currently used as an alternative treatment to CNI in the maintenance regimen of kidney transplant patients

may decrease extrarenal manifestations,

- **attenuate CNI toxicity and**
- **stabilise allograft function,**
- **providing a better alternative to CNI regimens**
- **ensure therapeutic adherence**

- *Belatacept conversion dosing was performed with a dose of 5 mg/kg belatacept every 2 weeks for a total of 10 weeks (five doses total), then monthly 5 mg/kg dosing.*

- *showed **no difference** in the rates of patient survival, graft survival, and acute rejection in **both low- and high-intensity** belatacept regimen groups compared with the CNI group*

- suggested that treatment with anti-thymocyte globulin (ATG) and MMF have a protective effect on recurrence

- activity such as:
- **elevated anti-dsDNA antibodies**
- **low complement levels**
- are reported to be unreliable predictors of relapse

work-up for the transplant

- work-up for the transplant candidate **does not differ** from the general guidelines recommended by the American Society of Transplantation and by the European Best Practice Guidelines for Renal Transplantation

Cardiovascular risk

- Patients with SLE have a higher risk of cardiovascular disease (including myocardial infarction, cerebrovascular disease, and peripheral vascular disease) compared with the general population
- Besides electrocardiogram and echocardiography, exercise thallium testing, sestamibi testing, exercise echocardiography, and/or dipyridamole echocardiography are all recommended.

- Patients at high risk (such as heavy smokers, those with severe left ventricular hypertrophy, severe hypertension, diabetes, previous cardiovascular events, and/ or long-term dialysis) should undergo a coronary angiography and should be treated with revascularization when needed.
- An angioMRN is indicated for patients who suffered from lupus cerebritis

- A search for antiphospholipid antibodies is recommended in SLE patients
- and
- should be mandatory in patients with a history of :
- vascular thrombosis,
- spontaneous abortion
- or preterm delivery

RECURRENT LUPUS NEPHRITIS POSTTRANS PLANTATION

- An important concern among patients with lupus nephritis (LN) who undergo kidney transplantation is the development of recurrent disease in the allograft.
- median time to recurrence was 4.3 years but can vary from five days post transplant to 16 years
- **most episodes occurring during the first 10 years**
- recurrence rate in the allograft can vary from 0-54% depending on various factors such as patient population, indication for renal biopsy, immunosuppressive regimen, and histological assessment

- This is due at least in part to the increased use of allograft biopsies and, in particular, the detection of subclinical recurrence by protocol biopsies

- recurrence is 18-30% when indication biopsies are examined with immunofluorescence (IF) and electron microscopy (EM) inaddition to light microscopy (LM)

- recurrence rate is even higher, that is, 43-54%, when protocol biopsies are performed and examined with the same histological methods

- In the largest reported series, the frequency and outcome of recurrence were analyzed using data from the United Network for Organ Sharing (UNOS) files

- Among 6850 patients with end-stage kidney disease (ESKD) due to LN who received a transplant between 1987 and 2006, 167 (2.4 percent) had recurrent LN.

- Reported rates of clinically apparent recurrent LN in the kidney transplant range from 2 to 11 percent
- rate of recurrent symptoms of systemic lupus erythematosus (SLE) is also low, at approximately 6 percent
- low rates are thought to reflect diminished immunologic activity in the setting of continuous immunosuppression.

- recurrence of lupus nephritis still remains a relatively rare cause of renal allograft loss

- low recurrence rate suggests that routine laboratory follow-up is not necessary and is only indicated in the case of signs or symptoms comparable with SLE disease activity.

Diagnosis of recurrent :

- Development of renal insufficiency and proteinuria was accompanied by a new butterfly rash,
- decreased serum complement levels,
- And
- a positive ANF

- any patient who develops increased proteinuria, hematuria, or an increased serum creatinine after transplantation

- do not routinely measure serologic parameters, such as:
- complement levels
- titers of anti-dsDNA antibodies,

- Serologic parameters and infrequent extrarenal symptoms of SLE may not accurately assess disease activity and do not help in predicting disease recurrence in the allograft

- Patients suspected of having recurrent LN should be evaluated using a similar approach to that used to evaluate kidney allograft dysfunction in other transplant recipients

- In such patients, it is important to exclude other potential causes of an increased serum creatinine, proteinuria, or hematuria, such as hypovolemia, calcineurin inhibitor toxicity, renal artery stenosis, pyelonephritis, or acute rejection.

- Patients who do not have an identifiable potential cause for allograft dysfunction frequently require a kidney allograft biopsy to establish a diagnosis.

- A kidney allograft biopsy with analysis of tissue by light, immunofluorescence, and electron microscopy is generally needed to make the diagnosis of recurrent LN

Treatment

- treatment of recurrent LN depends upon the clinical presentation and findings on the kidney biopsy.

Renin-angiotensin system inhibition

- all patients with recurrent LN who have proteinuria >500 mg/day, even in the absence of hypertension

- suggest treating with renin-angiotensin system (RAS) inhibition (either an angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]) to reduce proteinuria and slow the progression of kidney disease

- Most studies are of ACE inhibitors, but it seems likely that ARBs have a
- similar renoprotective effect as ACE inhibitors in nondiabetic CKD.
- ACE inhibitors and ARBs may cause hyperkalemia and decreased perfusion among transplant recipients.
- also induce or worsen anemia in transplant Recipients

Modification of immunosuppression

- Most patients with recurrent lupus nephritis, particularly those who have mild lesions on allograft biopsy, do not require any change in the immunosuppressive regimen that was used to prevent rejection.

- Selected patients, particularly those with more severe disease, may require modification of their antirejection immunosuppression regimen to treat recurrent LN

Our approach to immunosuppression is as follows:

Patients with recurrent LN who have mild lesions (class I or II LN) on allograft biopsy do **not** require a change in the maintenance immunosuppressive regimen used to prevent rejection

- patients with recurrent LN who have focal or diffuse (class III or IV LN, respectively) lesions on allograft biopsy:

- suggest escalating the maintenance immunosuppression regimen to treat LN

- Induction therapy options for LN in the native kidney primarily include mycophenolate mofetil (MMF) and cyclophosphamide.
- no high-quality studies that have examined the efficacy of these agents in transplant recipients with recurrent LN

- Options for immunosuppression modification include the following:
- Increase the dose of MMF to 2000 to 3000 mg/day (or 1440 to 2160 mg/day of EC-MPS).
- If the patient is on azathioprine (rather than MMF/ECMPS), discontinue azathioprine and switch to MMF or EC-MPS.

- induction dosing of mycophenolate should be continued for six months before being reduced to conventional maintenance dosing.

- **Or:**
- Administer cyclophosphamide and discontinue the current antimetabolite (usually MMF/EC-MPS or azathioprine).
- optimal cyclophosphamide dose for the transplant recipient is not known, and no studies have examined this issue.
- use the same regimen as use in the native kidney.
- After approximately three to six months, cyclophosphamide is replaced by the mycophenolate dose used for transplant rejection prophylaxis

- treated with an increase in glucocorticoids
- give a pulse of intravenous (IV) methylprednisolone, usually 250 to 500 mg for one to several days followed by a tapering oral glucocorticoid regimen that,
- over three to four months, returns to a previous maintenance glucocorticoid dose (eg, prednisone 5 mg daily).

- Response to therapy is monitored similarly to that for LN in the native kidney
- includes serial evaluation of serum creatinine, proteinuria, and
- hematuria
- In addition,
- many centers will perform repeat allograft biopsies after six months to assess histologic responses and confirm

- **If treatment with mycophenolate or cyclophosphamide is ineffective** :
- some clinicians give rituximab in addition to mycophenolate
- with or without an increase in glucocorticoids

- no published studies that support the use of rituximab for recurrent LN among transplant recipients.

- ***optimal dose of rituximab for recurrent LN is not known***.
- 1000 mg given on days 1 and 15, the US Food and Drug Administration [FDA]-approved dosing scheme for use in rheumatoid arthritis patients)
- some centers use the FDA recommended dose for anti neutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis (375 mg/m2 per week for four weeks)
- suggests giving one dose of rituximab 200 mg, based upon the dose used in studies of patients undergoing ABO-incompatible transplantation

Prognosis

- incidence of graft loss due to recurrent LN is low, being less than 2 to 4 percent over 5 to 10 years in most studies

- There is agreement that the histological lesions in grafts with recurrence are usually not severe
- Most patients have :
- minimal mesangial (class I),
- mesangial proliferative (class II),
- focal LN (class III),
- not diffuse LN (class IV),

- presence of milder histologic lesions is likely related to ongoing immunosuppression from the time of transplantation and is consistent with the generally good long-term kidney prognosis in patients with recurrent LN.

- In addition,
- majority of patients who develop impaired kidney function have one or more other histologic findings including :

- acute rejection,
- chronic allograft nephropathy,
- calcineurin inhibitor nephrotoxicity

infection,

- Another explanation could be a higher rate of infection, due to the use of immunosuppressive medication,
- Prior therapies used for LN (eg, prior cyclophosphamide and other immunosuppressive agents) may influence the risk of transplant marrow suppression such as progressive multifocal leukoencephalopathy (PML).
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Malignancy risk

- Solid organ transplant recipients have a higher risk of malignancy compared with the general population
- risk appears to be higher among patients who have received immunosuppressive medications prior to transplantation, such as those with systemic lupus erythematosus (SLE)
- Non transplant patients with SLE have been shown to have an increased risk of overall cancers,
- among kidney transplant recipients, the risk of most malignant tumors (except melanoma) appears to be similar between patients with SLE and those without SLE

- Kidney transplantation has been associated with a reduction in risk of cardiovascular events

- In a cohort study of 5963 patients with ESKD due to LN, of whom 3209 (54 percent) received a kidney transplant, kidney transplantation was associated with a lower risk of myocardial infarction and stroke compared with maintenance dialysis.