Kidney Transplantation in Lupus Nephritis

Gathered by:
Maryam Hami MD
Professor of Nephrology
Mashhad University of Medical Sciences

- Approximately 10 to 30 % of patients with LN progress to ESKD, depending upon:

1. the severity of the disease
2. ancestral and socioeconomic factors
3. nonadherence to treatment
4. response to initial treatment.

- Kidney transplantation has been safely performed in patients with ESKD due to LN and is associated with improved patient survival.

Lupus Nephritis and Kidney Transplantation. Adv Chronic Kidney Dis 2019; 26:313

Lupus activity in patients with ESKD

- The development of ESKD is, in many patients, associated with gradual complete or partial resolution of the extrarenal manifestations of SLE.
- In one literature review, the percentage of patients with active clinical lupus fell from 55 % at the onset of dialysis to 6.5 %in the 5 year and, in a small number of patients, to 0 % in the 10 year.
- In one study, the number of patients with severe extrarenal activity (defined by a SLEDAI >10) declined from 17 to 3 after the initiation of dialysis and to zero after transplantation.
- How these changes occur is not clear but may relate to modifications of the immune system with prolonged ESKD.

Ann Intern Med 1991; 114:183

- During this time span, the incidence of serologic activity (defined as the percentage of patients with two or more abnormal studies for ANA, anti-dsDNA, CH50, or C3) fell from 80 to 22%.
- However, some investigators contend that the observation that SLE becomes quiescent with the onset of ESKD is exaggerated and that up to one-quarter of patients on dialysis may continue to have extrarenal manifestations including alopecia, arthritis, myositis, pleuritis, pericarditis, fever, thrombocytopenia, leukopenia, and vasculitis.
- These contradictory observations may be due in part to varying patient populations and the clinical specialty of the examining physician.

Disease Flare of SLE in Patients With ESKD. J Rheumatol 2022; 49:1131

Kidney transplantation for lupus nephritis

- LN accounts for approximately 2% of the United States kidney transplantation population.
- Several studies have shown that patients with SLE and ESKD have a lower rate of preemptive transplantation than those with other forms of glomerular disease such as IgA nephropathy.
- Transplantation should be discussed as a treatment option with all patients with SLE and ESKD unless clear contraindications exist.

Update on Lupus Nephritis: Core Curriculum 2020. Am J Kidney Dis 2020; 76:265

Timing and type of transplantation

- How long a patient who has ESKD due to LN should wait prior to kidney transplantation has been a controversial issue in the past.
- Based on evidence of better outcomes in patients with a shorter duration of dialysis, KDIGO clinical practice guidelines recommend transplantation as soon as the disease is quiescent.
- We suggest not setting an arbitrary waiting time on dialysis before transplantation for most patients with SLE.
- Patients who have a potential living donor should undergo preemptive transplantation provided their extrarenal manifestations of SLE, if present, are deemed stable for surgery.

Update on Lupus Nephritis: Core Curriculum 2020. Am J Kidney Dis 2020; 76:265

- In the past, a 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".
- However, studies have shown that increased waiting time, particularly while on dialysis, is associated with worse graft outcomes after transplantation.

Update on Lupus Nephritis: Core Curriculum 2020. Am J Kidney Dis 2020; 76:265

- A study of over 8000 patients with ESKD due to LN showed improved graft and patient survival among those who underwent preemptive kidney transplantation compared with those who were on dialysis before transplantation .
- The presence of serologic disease activity at the time of transplantation has not been shown to correlate with transplant outcome.

The utility of lupus serology in predicting outcomes of renal transplantation in lupus patients: Systematic literature review and analysis of the Toronto lupus cohort. Semin Arthritis Rheum 2017; 46:791.

Immunosuppressive 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, although the use of glucocorticoid-free regimens among patients with ESKD due to LN is not standard practice.
- Moreover, prior therapies used for LN (eg, prior cyclophosphamide and other immunosuppressive agents) may influence the risk of transplant marrow suppression and infections such as progressive multifocal leukoencephalopathy (PML) due to JC polyoma virus.

Presence of antiphospholipid antibodies

- aPL are detected in up to 40% of patients with SLE; however, the development of APS is much less common.
- Patients with SLE who also have aPL are at increased risk for thrombotic events, including the development of TMA 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.

Antiphospholipid antibodies and renal transplant: A systematic review and meta-analysis. Semin Arthritis Rheum 2019; 48:1041.

- The optimal therapy of patients with aPL but without a history of a thrombotic event is not well defined.
- There are different protocol in centers:

1. low-dose aspirin (81 mg daily)
2. oral vitamin K antagonists

- The 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.

n engl j med 371;4 nejm.org july 24, 2014

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 24, 2014 VOL. 371 NO. 4

Inhibition of the mTORC Pathway in the Antiphospholipid Syndrome

Guillaume Canaud, M.D., Ph.D., Frank Bienaimé, M.D., Ph.D., Fanny Tabarin, M.S., Guillaume Bataillon, M.D., Danielle Seilhean, M.D., Laure-Hélène Noël, M.D., Marie-Agnès Dragon-Durey, M.D., Ph.D., Renaud Snanoudj, M.D., Ph.D., Gérard Friedlander, M.D., Ph.D., Lise Halbwachs-Mecarelli, Ph.D., Christophe Legendre, M.D., and Fabiola Terzi, M.D., Ph.D.

ABSTRACT

BACKGROUND

Although thrombosis is considered the cardinal feature of the antiphospholipid syndrome, chronic vascular lesions are common, particularly in patients with life-threatening complications. In patients who require transplantation, vascular lesions often recur. The molecular pathways involved in the vasculopathy of the antiphospholipid syndrome are unknown, and adequate therapies are lacking.

From INSERM Unité 1151, Institut Necker–Enfants Malades, Université Paris Descartes, Sorbonne Paris Cité (G.C., F.B., F.T., G.F., L.H.-M., C.L., F.T.), Service de Néphrologie Transplantation Adultes (G.C., R.S., C.L.), Service de Physiologie–Explorations Fonctionnelles (F.B., G.F.), Service

- Canaud et al identified the mTORC (mechanistic target of rapamycin complex) pathway as a potential intermediate and a therapeutic target in chronic vascular lesions associated with APS nephropathy.
- The authors demonstrated endothelial activation of the mTORC pathway in the renal microvasculature of patients with APS nephropathy and its association with the proliferation of both endothelial and vascular smooth muscle cells.
- They also suggested that the mTOR inhibitor sirolimus reduces the risk for recurrence and improves allograft survival in patients with APS nephropathy who required kidney transplantation.

Cell. Volume 149,2012; 274-293

OUTCOMES AFTER TRANSPLANTATION

- **Patient and allograft survival** — Kidney transplantation has been associated with improved survival among patients with ESKD due to LN.
- In an analysis of 20,974 patients diagnosed with ESKD due to LN, kidney transplantation, compared with no transplantation, was associated with a 70 % reduction in all-cause mortality. This difference was largely explained by a lower risk of cardiovascular death and death from infection.
- Most studies have found that overall 5- and 10- year graft survival rates are similar among patients with LN compared with those in patients with other glomerular diseases.

Long-term renal survival of paediatric patients with lupus nephritis. Nephrol Dial Transplant 2022; 37:1069

Malignancy risk

- Solid organ transplant recipients have a higher risk of malignancy compared with the general population, and this risk appears to be higher among patients who have received immunosuppressive medications prior to transplantation, such as those with SLE.
- Nontransplant 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.
- At present, surveillance for malignancies should be similar to that for other transplant recipients.

Standardised incidence ratios (SIRs) for cancer after renal transplant in systemic lupus erythematosus (SLE) and non-SLE recipients. Lupus Sci Med 2016; 3:e000156.

Cardiovascular risk

- Patients with SLE have a higher risk of cardiovascular disease compared with the general population.
- Patients with ESKD due to LN have an increased risk of cardiovascular events (MI, ischemic stroke, or cardiovascular or cerebrovascular death) compared with patients with other causes of ESKD, with the exception of diabetic kidney disease.
- Kidney transplantation has been associated with a reduction in risk of cardiovascular events in such patients.

Cause of kidney disease and cardiovascular events in a national cohort of US patients with ESRD on dialysis: a retrospective analysis. Eur Heart J 2019; 40:887

RECURRENT LUPUS NEPHRITIS POSTTRANSPLANTATION

- Clinically apparent recurrent LN in the kidney transplant range from 2 to 11%. These low rates are thought to reflect diminished immunologic activity in the setting of continuous immunosuppression.
- In data from the UNOS files, among 6850 patients with ESKD due to LN who received a transplant between 1987 and 2006, 167 (2.4%) had recurrent LN. Rejection was much more common, occurring in 1770 patients (26%).
- Risk factors for recurrence are:

1. Non-Hispanic Black individuals
2. Females
3. younger recipients (33 years or younger)

- Higher rates of recurrence (ranging from 30 to 54%) have been reported in some studies. This is due at least in part to the increased use of allograft protocol biopsies in the detection of subclinical recurrence.

Recurrent lupus nephritis after kidney transplantation: a surveillance biopsy study. Ann Rheum Dis 2010; 69:1484.

- On kidney biopsy, the histologic lesion may be different and is often less severe from that observed in the native kidney, as is illustrated by the following observations:
- In the native kidneys, the predominant lesion was either a proliferative glomerulonephritis (class III or class IV) or membranous nephropathy (class V).
- By contrast, in the transplanted kidneys, the nephritis was most often only a mesangial lesion (class II), with just three patients having proliferative lesions.

Risk factors and impact of recurrent LN in patients with SLE undergoing renal transplantation: data from a single US institution. Arthritis Rheum 2009; 60:2757.

Clinical presentation

- Patients with recurrent LN posttransplantation generally present with an increased serum creatinine above their usual baseline, new-onset or worsening proteinuria of a variable degree, and new-onset hematuria on routine screening.
- Serologic markers such as low complement and high anti- dsDNA antibody titer have not been found to be reliable predictors of recurrence.
- Recurrent LN can occur as early as the first week to as late as 16 years after transplantation (median 4.3 years), with most episodes occurring during the first 10 years.

Recurrence of lupus nephritis after kidney transplantation. J Am Soc Nephrol 2010; 21:1200.

Evaluation and diagnosis

- 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.

Treatment

- The treatment of recurrent LN depends upon the clinical presentation and findings on the kidney biopsy.
- RAS inhibition — For all patients with recurrent LN who have proteinuria >500 mg/day, even in the absence of hypertension, RAS inhibition (either an ACE inhibitor or ARB) to reduce proteinuria and slow the progression of kidney disease is recommended.
- However it is less clear if RAS inhibition has a protective effect among proteinuric transplant recipients.
- Their adverse effects consist hyperkalemia and decreased perfusion also induce or worsen anemia among transplant recipients.
- There is limited data on the use of SGLT2 inhibitors to treat clinical kidney disease in transplant patients with LN.

Modification of immunosuppression

- 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. Such patients can generally be managed with a RAS inhibitor to reduce proteinuria and control blood pressure.
- For patients with recurrent LN who have focal or diffuse (class III or IV LN, respectively) lesions on allograft biopsy, escalating the maintenance immunosuppression regimen to treat LN is recommended.

- Induction therapy options for LN in the native kidney primarily include MMF and cyclophosphamide, with or without the addition of belimumab or voclosporin.
- There are no high-quality studies that have examined the efficacy of these agents in transplant recipients with recurrent LN.
- Most transplant recipients receive MMF or EC-MPS and a calcineurin inhibitor (tacrolimus or cyclosporine) as part of their antirejection immunosuppression regimen.

- Options for immunosuppression modification include the following:

1. 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, we discontinue azathioprine. This initial therapy dosing of MMF should be continued for six months before being reduced to subsequent therapy dosing.
2. Administer cyclophosphamide and discontinue the current antimetabolite (usually MMF/EC-MPS or azathioprine). The optimal cyclophosphamide dose for the transplant recipient is not known.

- It is recommended to use the same regimen as we use in the native kidney. After approximately three to six months, cyclophosphamide is replaced by the mycophenolate dose used for transplant rejection prophylaxis, which also serves as ongoing therapy for recurrent LN.

- Patients should also be treated with an increase in glucocorticoids. We generally give a pulse of 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 and 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 that activity of the recurrence has significantly declined after induction therapy.

- If treatment with mycophenolate or cyclophosphamide is ineffective, some clinicians give rituximab in addition to mycophenolate dosed at 2 to 3 g/day, with or without an increase in glucocorticoids.
- There are no published studies that support the use of rituximab for recurrent LN among transplant recipients.
- If used, the optimal dose of rituximab for recurrent LN is not known. It is suggested:

1. 1000 mg given on days 1 and 15, the FDA-approved dosing scheme for use in rheumatoid arthritis patients).
2. use the FDA recommended dose for ANCA-associated glomerulonephritis (375 mg/m2 per week for four weeks).

Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012; 64:1215.

- For recurrent LN in the allograft there are insufficient data to support the addition of either belimumab or voclosporin, both of which have been approved by the FDA for the treatment of LN.

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med 2020; 383:1117

Prognosis

- The incidence of graft loss due to recurrent LN is low, being less than 2 to 4% over 5 to 10 years in most studies.
- Most patients have minimal mesangial (class I), mesangial proliferative (class II), or focal LN (class III), not diffuse LN (class IV), which is the most severe form of LN and is associated with a worse prognosis.
- The majority of patients who develop impaired kidney function have one or more other histologic findings that could have contributed to progressive disease, including acute rejection, chronic allograft nephropathy, and calcineurin inhibitor nephrotoxicity.

A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int 2019; 95:219.