Management of lupus nephritis

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ABSTRACT

The severe and recurrent signs of a systemic form of lupus is lupus nephritis (LN). Keeping chronic kidney disease (CKD) at rest is the primary objective of LN care. The prognosis and quality of life for people with systemic lupus nephritis are significantly affected by the onset of LN, which impacts up to 60% of them. In more recent years, new medications that stop the progression of kidney damage and particular pathways have been identified, and the method for diagnosing to LN has been improved. Restoring normal renal function or, at least, stopping the progressive loss of kidney function is the primary goal of treatment for lupus nephritis. Depending on the type of lesion, numerous treatments are used. Another multisystem autoimmune ailments that often affects the kidneys is systemic lupus erythematosus. The most frequent cause of damage to kidneys among individuals having systemic lupus erythematosus is lupus nephritis (LN), that additionally presents an elevated risk for morbidity as well as mortality. The cause of lymphoplasma is varied. This heterogeneity is probably caused by environmental as well as genetic variables. Although our understanding of the pathogenesis of LN has grown, here have been few improvements in treatment, and the risk of kidney failure remains too high. The present version of the Core Curriculum of Nephrology provides an in-depth discussion of the most recent information about the pathophysiology, diagnosis, medical treatment, and epidemiology of LN.

Keywords: lymphoplasma, systemic lupus nephritis,

INTRODUCTION

Since one of the distinctive facial SLE rashes depicts a wolf's bitemark, the term "lupus" is derived from the Latin term for "wolf." Hippocrates, the "father of medicine," documented the first appearance of lupus approximately 400 BC. It became debated throughout 1700 to 1800s as to whether lupus was linked to syphilis or tuberculosis. From being conceived of as just a cutaneous sign, lupus has evolved into a multisystemic condition that impacts all parts of the body. More than half of patients with systemic lupus erythematosus (SLE) possess lupus nephritis. Patients with this condition experience greater rates of morbidity and death due to, among other things, they have a tendency more likely to acquire chronic kidney disease, requiring renal replacement therapy in around twenty-five. But in addition to help improve outcomes with lupus nephritis patients, early and accurate determination of the condition as well as prompt beginning of treatment are critical. Type-3 hypersensitivity responses, which result in the growth of immune-mediated complexes, are the primary root cause of it. An immune-mediated complex referred to as anti-dsDNA is produced whenever

anti-double-stranded DNA (anti-dsDNA) assigns to DNA. These immune complexes reside in close proximity of the kidney's glomerular basement membrane on the mesangium, subendothelial, and/or subepithelial regions. As a result, the immune system's complement response is activated, provoking an influx of neutrophils and other inflammatory cells and the occurrence of lupus nephritis, a response to inflammation. Despite lupus nephritis is mainly brought about through an immune system response, an SLE patient may also be susceptible to having it through heredity. For instance, mutations in the APOL1 gene found just in African American populations with SLE and polymorphisms in the allele coding for the immunoglobulin receptors on macrophages were associated to a propensity to lupus nephritis..[1,2,3,4,5,6,7]

EPIDEMIOLOGY

Approximately 40% of individuals with systemic lupus erythematous (SLE) additionally suffer from lupus nephritis (LN). Immune-suppress medication improvements have significantly improved the long-term outlook of LN patients. There is evidence indicating that the 2000s witnessed a plateau in the improvement of LN outcomes. For the previous ten years, the incidence of developing LN-related end-stage renal disease (ESRD) at 5 ten, and 15 years of age remained 11%, 17%, and 22% (95% confidence intervals [CI]: 10%–12%, 16%–18%, 20%–23%) with current induction and maintenance sessions.

.[8,9,10]

LUPUS NEPHRITIS STAGES

A healthcare provider might identify the stage or classification of lupus nephritis based on the findings of the kidney biopsy. The six classes, or stages, are based on:

A less severe form of mesangial lupus nephritis, or

CLASS-1

The kidneys typically are not seriously harmed in this classification. There are however no obvious signs or indicators.

Proliferative mesangial lupus nephritis, is referred to as class 2,

CLASS- 2 will demonstrate some impairment of the kidneys. Furthermore, they may be tiny amounts of protein, blood, or both in the urine. Furthermore, they may be tiny amounts of protein, blood, or both in the urine.

Classified as localized lupus nephritis,

CLASS- 3.

The first group pertains to an injury to the kidney that impacts less than 50% of the glomeruli. Additionally, there will be higher amounts of blood, protein, or both in a person's urine. Further, they may have tachycardia.

Class 4, or diffuse lupus nephritis

Class 4 involves damage to more than half of the glomerulus. A person will have high blood pressure. They may require dialysis as kidney function begins to worsen.

Class 5, or membranous lupus nephritis

This classification involves thickening and scarring of the important structures within the kidney. A person will have high levels of blood, protein, or both in their urine as well as high blood pressure. They may also require dialysis or a kidney transplant.

Class 6, or advanced sclerosing lupus nephritis

This is the final classification. It involves damage to more than 90% of the important blood vessels in the kidney. A person will likely require dialysis or a kidney transplant.[11] clinical features The diversity of the clinical presentations of LN ranges from asymptomatic hematuria/proteinuria, hypertension, overt nephritic and nephrotic syndromes, rapidly progressive glomerulonephritis, and ESRD needing renal replacement therapy[12]. LN, like other more severe manifestations of SLE, is more common in African Americans, Asian/Pacific Islanders, and Hispanic patients[13]. There are risk factors that help us identify patients at an elevated risk of developing end-stage renal disease. Some risk factors are demographic, like male sex, young age, and African or Hispanic ethnicity; some are clinical, like anemia, elevated serum creatinine, and hypertension on the biopsy time ; and some are histopathological, like proliferative nephritis (class III or IV) and high chronicity or activity indices. It must be noted that the clinical phenotype cannot predict the class of LN. For example, in a series of 21 patients with SLE and isolated urinary abnormalities, the biopsies of 13 patients showed LN class III, IV, or V.[14_16] PATHOPHYSIOLOGY OF LUPUS NEPHRITIS SLE is a chronic inflammatory and autoimmune disease[17,18]. Systemic autoimmunity can lead to damage to tissues and organs; commonly, the kidney is injureous In patients with certain genetic polymorphisms (eg, those involved in DNA clearance, the complement pathway), exposure to specific environmental triggers can precipitate autovaccination against endogenous nuclear material and development of SLE[17_19]

A form of glomerulonephritis, LN can occur as a result of autoantibody-containing immune complex accumulation, local complement activation, leukocyte recruitment, and intrarenal cytokine signaling, which can lead to inflammation of the kidneys and contribute to glomerular and tubulointerstitial damage[17_19,22] The location of immune complex accumulation and complement activation determines the type of glomerular cell that is preferentially injured, defining the different histopathological classes of lupus nephritis (please see page 5 of this publication)[19,22].

Continued kidney inflammation can result in renal cell loss and nephron atrophy Episodes of increased disease activity, called renal flares, typically result in irreversible nephron loss that severely shortens renal life span[21,23].Nonimmune mechanisms of renal damage include disruption of cell-to-cell interactions, compromising the maintenance of nephron structures. Abnormal vascular function leads to tissue hypoxia and tubular atrophy, and renal fibrosis results from ischemia and hypertension. As nephron atrophy continues, compensatory hyperfiltration and other mechanisms in the remaining nephrons cause a rise in intraglomerular pressure and glomerular stress. Independent of SLE disease activity, compensatory hyperfiltration and consequent increases in nephron loss may occur, driving progression of CKD.[17,21]

ANTIBIOTICS AND APOPTOSIS OF LUPUS NEPHRITIS

Lupus nephritis is characterized by renal deposition of immune complexes. IgG antinuclear autoantibodies against components such as DNA and nucleoprotein are commonly found in the glomeruli and serum of individuals with lupus nephritis [23]. Circulating immune complex antibodies have been shown to more readily bind DNA but not glomerular basement membrane antigens whereas IgG from the glomeruli of SLE patients readily bound DNA, glomerular basement membrane antigen, proteoglycan, and heparan sulfate [24]. However, after treatment with heparitinase glomerular deposition of IgG was decreased, indicating potential direct glomerular basement membrane binding and immune complex formation through heparan sulfate by some anti-DNA autoantibodies [24]. *In vitro*, nucleosome and C1q deposition to glomerular endothelial cells is at least partially mediated by surface heparan sulfate and allows for subsequent binding of autoantibodies against nucleosomes that may be pathogenic and the autoantibodies against the C1q may further drive pathogenesis [25]. Conversely, after passage through Sepharose with glomerular basement membrane antigen, renal eluates lost the ability to bind glomerular basement membrane but still possessed the ability to bind DNA indicating a role for circulating immune complex glomerular deposition, suggesting that both mechanisms of deposition may play a role in lupus nephritis pathogenesis [24].

The ability to form immune complex depositions and where said immune complexes are formed varies based on the individual autoantibody involved [26]. In mouse models using various anti-DNA antibodies, mesangial and subendothelial immune complex depositions were correlated with proliferative glomerulonephritis, neutrophil infiltration, and proteinuria; diffuse fine granular mesangial and extraglomerular vascular immune complex depositions were correlated with proliferative glomerulonephritis and proteinuria; dense

intramembranous and intraluminal immune complex depositions were correlated with thickening of the capillary walls, mesangial interposition, mesangial expansion, aneurysmal dilatation, blockage of the capillary loops of the glomeruli within the lumen, and extensive proteinuria; and mesangial and extraglomerular vascular immune complex deposition correlated with slight segmental mesangial expansion and no associated proteinuria [26].

DIAGNOSIS
The diagnosis of lupus nephritis begins with a medical history, physical exam, and evaluation of symptoms. And other tests tests to make or confirm a diagnosis. Tests used in diagnosing kidney problems include urine tests, blood tests, imaging tests such as ultrasound, and kidney biopsy. In case of suspicion of LN, the proteinuria threshold at which a kidney biopsy is indicated is not defined. In practice, this procedure is proposed when the proteinuria level is ≥500 mg/day. Observational data show that proteinuria between 500 and 1000 mg/day is already associated with significant kidney damage [27] and also that "low-grade" proteinuria does not exclude significant kidney injury in LN [28].

Standard treatment of severe lupus nephritis

Increased awareness of severe forms of LN can help to improve the treatment and outcome. According to the Joint EULAR/ERA-EDTA, patients with class III or IV LN and high activity index should start therapy with three intravenous (iv) methylprednisolone pulses (MPP) and an immunosuppressive agent, mycophenolate mofetil (MMF) or cyclophosphamide (CYC). After MPP, patients should receive oral prednisone at progressive lower dosage (29). The Aspreva Lupus Management Study (ALMS) demonstrated that 3 g of MMF and monthly iv CYC pulses have the same efficacy and similar side effects in Caucasians and in Asian patients while in "other ethnicities", including African-Americans and Hispanics participants, MMF was significantly more effective than CYC (30). After these results, MMF became the drug of choice in LN patients with these ethnicities. However, in the ALMS, only half of patients achieved response at six months, defined as ≥50% reduction of proteinuria and stabilization of renal function (31).

First line therapy for patients with severe lupus nephritis.

Induction therapy
- **Class III/IV lupus nephritis**
- Intravenous (IV) pulse methylprednisolone (500 mg to 1 g) daily for 3 days followed by prednisone 1 mg/kg/ day (crescents on biopsy) or 0.5 mg/kg/day (no crescents). Taper after few weeks to lowest effective dose
- Mycophenolate mofetil (MMF) 2–3 g/day for 6 months **or** cyclophosphamide (CYC) in 2 different regimens:
- High-dose IV regimen (500–1000 mg/m2 monthly × 6 doses)
- Low-dose IV regimen (Euro-lupus: 500 mg IV every 2 weeks × 6 doses)
- Patients who fail improving on MMF, switching to CYC is considered. Patients who fail to respond to CYC consider switching to MMF.
- In patients who fail responding to both, they are candidates for rituximab, calcineurin inhibitors (cyclosporine, tacrolimus), or a combination of calcineurin inhibitors and low-dose MMF.
- The combination of MMF with a calcinurine inhibitors (CNI) (especially tacrolimus (TAC) might be a therapeutic option, especially in nephrotic-range proteinuria
- **Anticoagulant therapy:** Anticoagulant therapy should be considered in nephrotic syndrome with heavy proteinuria and serum albumin less than 20 g/L. class 5 lupus nephritis
- Oral prednisone 0.5 mg/kg/day for 6 months; **plus** MMF 2–3 g/day for 6 months
- Calcineurin inhibitors (cyclosporine/tacrolimus) can be added to MMF: use caution in patients with renal insufficiency or hypertension.
- IV CYC if other therapies fail
1. B)
Adjunctive therapies
- Hydroxychloroquine
- Angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) if proteinuria ≥0.5 g/24 h
- Control blood pressure (BP): should be ≤130/80
- Statin therapy if low-density lipoprotein (LDL) cholesterol >100 mg/dL

- Stop smoking

DRUGS USED IN LUPUS NEPHRITIS

1. I.

Cyclophosphamide

- The two commonly recommended IV regimens are as follows:
- **High dose:** Monthly boluses of 0.5–1.0 g/m2 IV × 6 months
- **Low dose** (Euro-Lupus protocol): 500 mg IV every 2 weeks × 6 doses
- Low-dose therapy is associated with fewer serious infections and less risk of infertility, but some patients may fail to respond to lower doses
- IV dosing regimens (compared with oral) result in a lower total CYC exposure, which is important when considering effects on fertility and bladder toxicity.
- Premature ovarian failure risks correlate with the cumulative dose of CYC (>10–15 g total dose) and the age of the patient (>30 years) [32].
- Anti-Mullerian hormone measurement can be used to determine ovarian reserve, but its clinical value is unclear.

Consider rituximab 1 g IV plus CYC 500–750 mg IV for resistant disease, followed by the same 14 days later.

- **Describe a protocol for using monthly IV CYC**

Level of evidence:1, GoR: A, mean+SD:8.57+1.12, percentage of agreement: 100%

Level of agreement: High

1. a)

Prior to CYC

- Premedication 15–30 min prior to CYC: dexamethasone 10 mg, and ondansetron (Zofran) 8 mg or ganisetron (Kytril) 1 mg in 100 cc normal saline IV
- Mesna (25% of CYC dose in milligrams) in 250 cc normal saline

2. b)

CYC infusion

- CYC 0.5–1.0 g/m^2 of a body surface area in 1000 cc normal saline for initial dose. If creatinine clearance is less than 35–40 cc/minute, then start initial dose at 0.5 g/m^2 of bovine serum albumin. If on dialysis, give 0.4–0.5 g/m^2 8–10 h before or after dialysis.

3. c)

Post CYC infusion

- Mesna (25% of CYC dose in mg) in 250 cc normal saline

4. d)

Follow-up patients for hematuria and cancer bladder whenever feasible.

5. e)

To prevent premature gonadal failure from long-term therapy, consider using gonadotropin-releasing hormone (Leuprolide) 3.75 mg intramuscularly (IM) 10 days prior to each monthly CYC dose or testosterone supplementation (200 mg IM every 2 weeks) for men (data is limited) [36].

- **e) Maintenance after the CYC course**
- Maintenance with AZA or MMF

1. II.

B cell therapy in lupus nephritis

o **Role of B cell depletion therapy**

Lupus nephritis is characterized by a complicated interplay of immunologic disturbances and renal damage caused by the development of pathogenic autoantibodies and immune complexes, which activate complement and cause inflammatory cell infiltration in the kidney. B lymphocytes are key players in this process because they are the progenitors of plasma cells, which create pathogenic autoantibodies, and they also serve as antigen presenters for T lymphocytes [33].

- **Rituximab (anti-CD20)**

Loading: 1 g on days 1 and 15

Maintenance dose: 500 mg IV every 6 months

- **Ocrelizumab (anti-CD20)**

The first dose is a 300-mg intravenous infusion given over 2.5 h, followed by another 300 mg intravenous infusion 14 days later.

Then, every 6 months, a 600-mg intravenous infusion is given over 3.5 h.

- **Obinutuzumab (anti-CD20)** [34]Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody that binds to the CD20 antigen in a different way than type I anti-CD20 antibodies (1000mg/40ml).
- **Epratuzumab (anti-CD22)**
  o Epratuzumab is a recombinant humanized monoclonal IgG antibody to CD22 that promotes antibody-dependent cellular cytotoxicity and depletes B cells. Epratuzumab is thought to alter B cell function without killing them; however, the exact mechanism of action is unknown.
  o **Targeting B cell survival factors**
- **Belimumab**

Indicated for active lupus nephritis in patients who are receiving standard therapy.

IV

Initial: 10 mg/kg IV q 2 weeks x 3 doses, THEN

Maintenance: 10 mg/kg IV q 4 weeks

SC

Initial: 400-mg dose (two 200-mg injections) sc q week x 4 doses, THEN

Maintenance: 200 mg sc q week thereafter. Transitioning from IV to SC dosing at any time after completing the first 2 IV doses.

If transitioning, administer first sc dose of 200 mg 1–2 weeks after the last IV dose [35].

- Atacicept

Atacicept inhibits B cell stimulation by binding to both BLys and a proliferation-inducing ligand (APRIL). Atacicept is thought to impair mature B cells and plasma cells while having little effect on progenitor and memory B cells.

MANAGEMENT OF LUPUS NEPHRITIS IN CHILDREN

Childhood-onset systemic lupus erythematosus (cSLE) has an incidence of 0.3 to 0.9 per 100,000 children-years and a prevalence of 3.3-8.8 per 100,000 children with higher prevalence rates in non-white populations including Asians [37]. About 10-20% of cases of SLE are diagnosed during childhood with a median age of onset of 11-12 years, and these patients have increased disease severity and lower survival rates [38]. Renal disease occurs in 50-75% of all cSLE patients, mostly within the first two years of diagnosis [38,39]. As per the American College of Rheumatology (ACR) criteria, lupus nephritis is defined as persistent proteinuria (>0.5 g/day or >3+ by dipstick) and/or cellular casts in the urine. A spot urine protein/creatinine ratio of >0.5 can be substituted for the 24-hour urine protein measurement and an 'active urinary sediment' (>5 RBC/high power field (hpf), >5 WBC/hpf in the absence of infection, or cellular casts limited to red blood cells or white blood cell casts) can be substituted for cellular casts [40]. Initial manifestations of renal disease range from minimal proteinuria and hematuria to nephrotic-range, rapidly progressive glomerulonephritis, severe hypertension, and acute kidney injury. The frequency of nephritis in patients with SLE is significantly higher in African Americans, Asians (40-82%) and Hispanics than in whites (29%) and is higher in men [41]. Nephritis is a major risk factor for morbidity and mortality in SLE and 10% of patients with lupus nephritis will develop end stage renal disease (ESRD) with a higher risk in patients with more severe histological classification (44% over 15 years) [5].

INDUCTION

THERAPY

The consensus treatment plans for induction therapy recommend either intravenous cyclophosphamide (IV-CYC) or mycophenolate mofetil (MMF) along with steroids for a duration of 6 months. Consensus was reached to administer a total of 6 monthly IV-CYC dosages (starting with 500 mg/m2 and increasing based on tolerance and WBC nadir to a maximum dosage of 1,500 mg). In the adult literature, this standard dosing regimen (designated the NIH regimen) has been compared to a low dose (or Euro-lupus) regimen which consists of 500 mg IV-CYC every 2 weeks for 6 treatments followed by initiation of maintenance therapy. These regimens have shown a similar efficacy in the populations studied and the ACR recommends this regimen for IV-CYC induction in patients who are white with European background[42]. The KDIGO guidelines also include option for oral cyclophosphamide (1.0-1.5 mg/kg/day, maximum 150 mg/day) for 2-4 months [43]. MMF is recommended at a dose of 600 mg/m2/dose (maximum 1,500 mg) twice daily. This is

similar to European pediatric consensus dosing regimens (1200 mg/m2/day, maximum 2000 mg/day; when poor response option to increase to maximum of 1800 mg/m2/day, maximum dose 3000 mg/day) [44]. African-Americans and Hispanics with lupus nephritis may respond less well to IV-CYC than patients of white or Asian races; thus, MMF is the preferred agent for these populations [43]. Observational studies and a recent single center trial from India suggest a comparable rate of response with either IV-CYC (both dosing regimens studied) or oral MMF [45_47]. However, one pediatric study in the Indian population detected better efficacy of MMF compared with IV-CYC induction [48].

Adjunctive therapy

Hypertension should also be addressed aggressively, as it can both be a symptom of LN and cause long-term renal disease. A renin-angiotensin-aldosterone system blockade is recommended in non-pregnant patients, as it has both antiproteinuric and antihypertensive effects [49]. Although all calcium channel blockers (CCBs) are equally effective in lowering blood pressure, non-dihydropyridine CCBs, such as diltiazem and verapamil, have the additional property of reducing proteinuria similar to angiotensin-converting enzyme inhibitors(ACEI) as well as slowing the decline in renal function [50].

Statin therapy should be considered on the basis of lipid levels in the active phase of LN and long-term cardiovascular risk factors. Statins have been shown to reduce proteinuria and thus are a useful adjunct [51]. In addition, statins may have other non-lipid-related immunosuppressive benefits, such as reduction in serum immunoglobulin G (IgG), anti-dsDNA Abs, and proteinuria [52], and can improve long-term outcomes in SLE [53].

Maintenance therapy

it has been best studied with MMF and azathioprine (AZA), each having different advantages and disadvantages. MMF is superior to AZA in maintaining remission [54], with neither drug showing superiority in the side-effect profile. In the United States due to the teratogenic side effects, MMF has a black box warning regarding its use in pregnancy. For clinical use, there are now in place shared risk evaluation and mitigation strategies to ensure the safe use of MMF [55]. Patients who achieve remission of LN and wish to conceive or become pregnant should be transitioned to AZA given the safety in pregnancy and fact that flares of LN on AZA remain rare [56].

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