

Advances in Diagnosis and Treatment of Lupus Nephritis (Class V)

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Abstract: Membranous lupus nephritis (MLN), class V, is a distinct LN characterized by immune complex deposition on subepithelial kidney biopsy. MLN is often associated with nephrotic syndrome. The histology of MLN is very similar to idiopathic (primary) membranous nephropathy (pMN). However, MLN usually has abundant mesa-glomerular deposits absent in primary membranous nephropathy. The clinical manifestations, management, and prognosis of MLN differ from other types of LN (type III, IV, or mixed type III/IV + V). Although immunosuppressive therapy is often necessary for MLN, the optimal treatment regimen is yet to be determined. This review summarizes the progress in the diagnosis and treatment of MLN and discusses the selection of immunosuppressants for MLN.

Keywords: Systemic lupus erythematosus; Lupus nephritis; Class V lupus nephritis

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1. Introduction

Systemic lupus erythematosus (SLE) is one of the most common diffuse connective tissue diseases, with an incidence of about 70/100,000^[1] and is increasing year by year. SLE is more common in women than men across all age groups and populations. SLE is a chronic inflammatory disease that can affect any organ, with kidney damage being the most common of all organs. According to statistics^[2], about 80% of SLE patients have clinical manifestations of renal involvement; almost 100% have varying degrees of renal disease; renal injury and progressive renal failure are among SLE's leading causes of death.

Lupus nephritis (LN) was defined as clinical and laboratory features meeting the criteria set by the American College of Rheumatology (ACR), i.e., persistent proteinuria > 0.5 g/d or more excellent (+++), and cellular types, including red blood cell and hemoglobin casts, granular casts, casts, or mixed casts. However, according to the 2012 ACR criteria, the gold standard for diagnosing LN is still immune complex-mediated glomerulonephritis confirmed by renal biopsy^[3]. In recent years, the International Society of Nephrology/Society of Nephrology 2003 LN classification criteria (**Table 1**) have also been unanimously recommended by the ACR and European Alliance of Associations for Rheumatology (EULAR)^[4].

Table 1. Classification criteria for lupus nephritis in 2003 by the International Society of Nephrology/
Society of Nephrology

Classification	Features
I (Minimally diseased LN)	Light microscopy is commonly employed for cases of mild membranous lupus nephritis. Immunofluorescence reveals mild deposition of immunopositive compounds on the membrane.
II (Mesangial hyperplastic LN)	In membranous proliferative lupus nephritis, membranous cells proliferate, and the matrix increases under the light microscope. Immunofluorescence shows that the deposition of immune complexes is limited to the membranous area.
III (Focal LN)	Focal proliferative lupus nephritis, proliferation of endothelial cells, deposition of immunopositive compounds under the endothelium, < 50% of glomeruli with cell proliferation, necrosis, and inflammatory changes.
IV (Diffuse LN)	Diffuse proliferative lupus nephritis, proliferation of endothelial cells, deposition of immunopositive compounds under the endothelium, and > 50% of glomeruli showing cell proliferation, necrosis, and inflammatory changes.
V (Membranous LN)	MLN, glomerular capillary basement membrane thickening, immune complex epithelial cell deposition.
VI (Advanced sclerosing LN)	Sclerosing lupus nephritis, more than 90% glomerulosclerosis, no active disease

Research on lupus nephritis at home and abroad has gradually deepened in recent years. Among them, LN (Class V), that is, MLN, as an end-stage severe lupus nephritis, is more severe than Class I–IV lupus glomerulonephritis but has not yet fully developed into Class VI LN. Hence, the condition is complex and changeable, and the treatment is more complicated. Clinically, MLN manifests as nephrotic syndrome, acute nephritis, or acute renal failure, and there is a great possibility of developing end-stage renal disease. Although the research on LN is deepening, the research on MLN is still lacking.

The LN guidelines were jointly developed by the European Society of Rheumatology and the European Society of Nephrology-European Association for Dialysis and Renal Transplantation (EULAR/ERA-EDTA). The ultimate goal of LN treatment is to protect renal function in the long term, prevent recurrence, and avoid treatment-related injuries, improve survival rate and quality of life. The goal of treatment should be complete renal remission, i.e., urine protein: protein/creatinine ratio (UPCR) < 50 mg/mmol (proteinuria < 0.5 g/24 hours) and glomerular filtration rate (GFR) is normal or near normal (if they were previously abnormal, within 10% of normal GFR). Partial renal remission: that is, the reduction of proteinuria by $\geq 50\%$, reaching or not reaching the range of nephropathy, and the glomerular filtration rate is average or close to normal. Better clinical results should be achieved within 6 and 12 months of treatment. Renal improvement: i.e., any reduction in urinary protein and normalization or stabilization of glomerular filtration rate. With LN (Class V), the goal is more of partial remission or improvement of the kidneys. Similar to other pathological LN, the treatment options for LN (Class V) can be divided into initial treatment, maintenance treatment, adjuvant treatment, and traditional Chinese medicine (TCM) treatment.

2. Initial treatment

For LN (Class V), based on a better efficacy/toxicity ratio, initial treatment can be glucocorticoid combined with mycophenolate mofetil (MMF) or high-dose intravenous injection cyclophosphamide (CYC), or cyclosporine (with a higher relapse rate in nephrotic syndrome), or tacrolimus in combination with oral therapy as initial treatment (Author, Year). The recommended dose is prednisone 0.5 mg/(kg·d)+ MMF (target dose three g/d, six months) combined with oral administration as initial treatment. Without a response, CYC or a

calcium-conditional phosphatase inhibitor (cyclosporin), or rituximab can be used as an alternative treatment. Azathioprine (AZA) can be an option in patients with no clinical and pathological prognosis for type V LN in non-nephrotic extensive proteinuria. AZA is used when MMF or CYC use is contraindicated, intolerable, or challenging. However, AZA has a higher risk of recurrence^[5]. Although the number of adverse events in the MMF group is similar to CYC, and its ability to preserve renal function long-term is unclear, MMF has replaced CYC as the first-line induction therapy for MLN in many areas.

In addition to the hormones and immunosuppressants mentioned above, some antineoplastic drugs have gradually been found to have unique effects on MLN in recent years. Proteasome inhibitors are mainly used in treating plasma cell malignancies. Still, their mechanism of action may play a two-step role in the pathogenesis of LN and kidney injury. The overall effect of borate proteasome inhibitors (such as bortezomib and carfilzomib) is to kill plasma cells, so these drugs immediately attenuate autoantibody production. This may prevent or reduce complex immune output, resulting in persistent immune complex-mediated kidney injury. More directly related to inflammation, proteasome inhibitors block the activation of NF- κ B and thus may also have anti-inflammatory effects. This class of drugs has successfully treated LN in mice^[6]. IFN- α appears to be a central regulatory cytokine in SLE, especially LN, and may promote the development of autoreactive plasma cells, helper and memory T cells, and several proinflammatory cytokines^[7-9]. Thus, blocking the action of IFN- α can improve inflammation, attenuate autoimmunity, and prevent future LN attacks. Anifrolumab, a monoclonal antibody against the IFN- α type 1 receptor, was influential in non-recurrent lupus and is currently being evaluated in a randomized clinical trial in LN.

3. Maintenance treatment

It is recommended that patients whose condition improves after the initial treatment continue to use immunosuppressive agents to consolidate the renal response and prevent relapse. LN (Class V) should be treated with MMF or AZA combined with low-dose corticosteroids for at least three years. The recommended dosage is 5 to 7.5 mg/d prednisone, 2 g/d MMF, 2 mg/(kg·d) AZA. When the condition of the patient is stable, the drugs are slowly withdrawn, and the glucocorticoid is first reduced. For patients who respond initially to MMF, MMF is continued during the maintenance period, and it is switched to AZA at least three months before pregnancy. In previous clinical studies, intrarenal inflammation is controlled during induction by high doses of corticosteroids, which are effective but toxic^[10]. Many adverse events during the first year of MLN treatment are likely attributed to corticosteroids, whose side effects often challenge patient compliance. Borrowing existing treatments for other diseases to treat kidney inflammation may reduce or eliminate the need for corticosteroids. In this case, C inhibitors, quinolone immunomodulators, and proteasome inhibitors should be considered for clinical treatment of MLN. Laquinimod, a quinolone, is a small molecule that blocks the activation of NF- κ B, a transcription factor essential for the expression of proinflammatory cytokines described in human multiple sclerosis^[11] and mouse LN^[12] studied. A small phase 2 trial in LN showed improved renal function and reduced proteinuria at six months when laquinimod was added to standard care, including corticosteroids^[13].

Simple MLN patterns can be applied to calcineurin inhibitors (CIN). The dose of MMF usually needs to be gradually reduced to reduce its toxicity (1 to 2 g/day can achieve long-term effectiveness). There have been no studies monitoring blood drug levels of MMF to minimize the harm of MMF while increasing its effectiveness. However, patients with a glomerular filtration rate < 30 mL/min should be monitored. For refractory MLN, a change in therapy from MMF to CYC or from CYC to MMF is recommended for those who fail to respond to MMF or CYC therapy, including lack of efficacy (as defined by LN immunosuppressive treatment goals) or

due to adverse effects. Those who cannot continue to take the drug are replaced with rituximab. Other options include CIN (cyclosporine, statins), intravenous immunoglobulin, plasmapheresis in acute nephritis, and immunoadsorption for other treatment failures or intolerance to other treatments.

4. Adjuvant therapy

(i) For patients with proteinuria (UPCR > 50 mg/mmoL) or hypertension, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor inhibitors can be used. (ii) For persistent lipid abnormalities, statin lipid-lowering drugs can be used to lower cholesterol levels, and the target value of low-density lipoprotein cholesterol (LDL-C) is 2.58 mol/L (100 mg/dL). (iii) Proper use of hydroxychloroquine improves patient outcomes by reducing renal recurrence and reducing renal and cardiovascular damage. Treatment with hydroxychloroquine is recommended for patients with all types of LN as long as there are no specific contraindications. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines pointed out that hydroxychloroquine can slow down renal injury in patients with LN, so the new guidelines recommend hydroxychloroquine as the primary treatment for LN ^[14]. Hydroxychloroquine at doses of 6.5 mg/(kg·d) or 400 mg/d is generally considered safe, with regular eye examinations recommended. After five years of treatment, annual eye examinations should commence. Individuals with risk factors for retinal damage should undergo yearly eye examinations from the time they begin taking the medication. (iv) Aspirin is used to prevent thrombosis in patients with antiphospholipid antibodies. (v) Anticoagulant therapy should be used for nephrotic syndrome and serum albumin < 20g/L, especially for persistent antiphospholipid antibodies.

5. TCM treatment

According to TCM syndrome differentiation, LM is based on a deficiency in origin and excess superficiality. Therefore, the primary treatment methods are removing heat and detoxification, promoting blood circulation, and removing blood stasis. According to clinical manifestations, Shen ^[15] divided LN into four types: yin deficiency and internal heat, yin deficiency, and heat depression, and deficiency of both qi and yin deficiency of both the spleen and kidney. In treating Yin-deficiency and internal-heat syndrome, clearing deficiency heat is the primary treatment; in yin deficiency and heat stagnation syndrome, nourishing the kidney and clearing heat is the immediate treatment. Ye ^[16] divided the disease into four types: flaming heat and toxin, spleen and kidney yang deficiency, yin deficiency and internal heat, and liver and kidney yin deficiency. For the burning heat-toxin type, the treatment is to clear away heat and detoxify, and cool the blood to stop bleeding using Xijiao Dihuang Decoction. For the spleen and kidney Yang-deficiency type, it is necessary to warm and invigorate the spleen and kidney, and dredge Yang Qi and the prescription is to use Zhenwu Decoction for treatment. Erzhi Pills or Buyin Pills can be added to cool the blood and stop bleeding. For liver and kidney Yin-deficiency type, Erzhi Pills can be added to nourish the liver and kidney, nourish yin, and clear away heat.

6. Conclusion

As scientific research advances, the diagnosis and treatment of LN, particularly MLN, are becoming increasingly standardized and optimized. However, clinical challenges persist. In all cases, the choice of a treatment plan should be based on various factors, including the patient's clinical condition, renal pathological activity indicators, the principle of chronicity, the patient's willingness and tolerance, as well as the presence of repeated infections, severe cytopenias, and renal function.

Disclosure statement

The authors declare no conflict of interest.

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