Membranous Lupus Nephritis Treatment

Dr.R.Abbasilarki

Nephrologist

YUMS

Kidney involvement is clinically apparent in approximately 50 percent of SLE patients and is a significant cause of morbidity and mortality.

Thus, periodic screening for lupus nephritis with urinalyses, quantitation of proteinuria, and estimation of the glomerular filtration rate is an important component of the ongoing management of SLE patients.

Several forms of glomerulonephritis can occur, and kidney biopsy is useful to define the type and extent of kidney involvement.

The clinical presentation of lupus nephritis is highly variable, ranging from asymptomatic hematuria and/or proteinuria to nephrotic syndrome and rapidly progressive glomerulonephritis with loss of kidney function.

Some patients with lupus nephritis also have hypertension.

Classification of Lupus Nephritis (International Society of Nephrology and Renal Pathology Society)

Class I: Minimal Mesangial Lupus Nephritis

Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.

Class II: Mesangial Proliferative Lupus Nephritis

Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.

Class III: Focal Lupus Nephritis

Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving ≤50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.

Class III (A): Active lesions—focal proliferative lupus nephritis

Class III (A/C): Active and chronic lesions—focal proliferative and sclerosing lupus nephritis

Class III (C): Chronic inactive lesions with glomerular scars—focal sclerosing lupus nephritis

Class IV: Diffuse Lupus Nephritis

Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than one-half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.

- Class IV-S (A): Active lesions—diffuse segmental proliferative lupus nephritis
- Class IV-G (A): Active lesions—diffuse global proliferative lupus nephritis
- Class IV-S (A/C): Active and chronic lesions—diffuse segmental proliferative and sclerosing lupus nephritis
- Class IV-G (A/C): Active and chronic lesions—diffuse global proliferative and sclerosing lupus nephritis
- Class IV-S (C): Chronic inactive lesions with scars—diffuse segmental sclerosing lupus nephritis
- Class IV-G (C): Chronic inactive lesions with scars—diffuse global sclerosing lupus nephritis

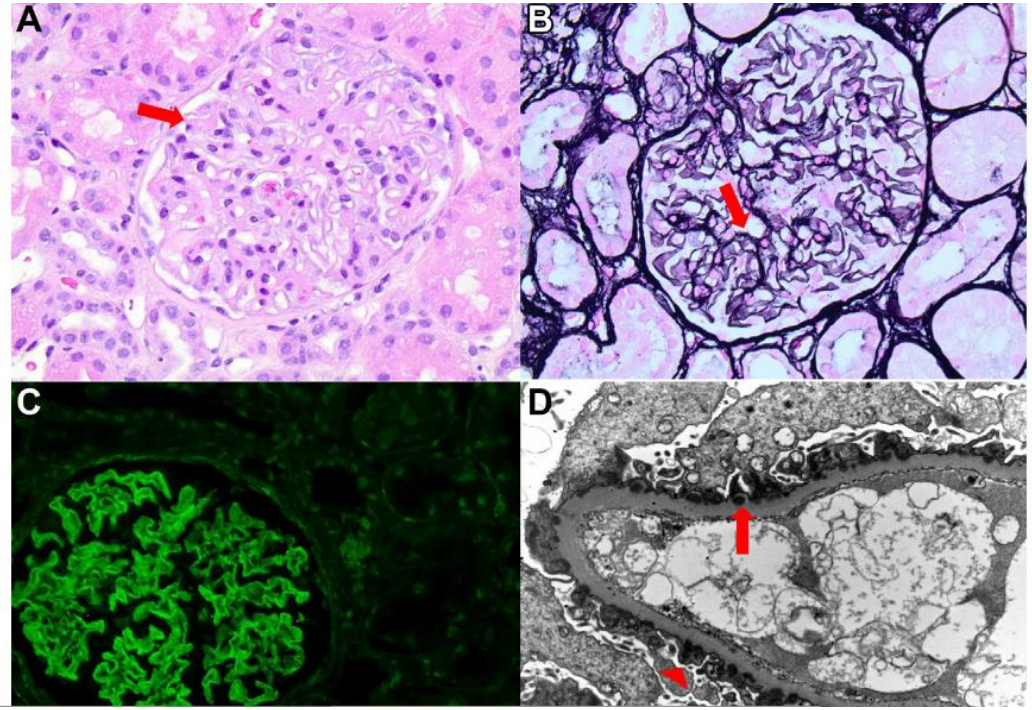
Class V: Membranous Lupus Nephritis

Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V lupus nephritis may occur in combination with class III or IV, in which case both will be diagnosed. Class V lupus nephritis may show advanced sclerosis.

Class VI: Advanced Sclerotic Lupus Nephritis

≥90% of glomeruli globally sclerosed without residual activity.

Membranous lupus nephritis (MLN) (Class V lupus nephritis [LN]) is a distinct form of LN defined by the presence of subepithelial immune complex deposits seen on kidney biopsy.



Histological findings in membranous lupus nephritis. (A) Light microscopy image demonstrating thickening of glomerular basement membrane (arrow). (B) Silver Jones stain demonstrating “spikes” of glomerular basement membrane in between immune complex deposits (arrow). (C) Diffuse granular pattern of IgG staining along the glomerular basement membrane. (D) Electron-dense deposits in the subepithelial space (arrow) with expansion of the glomerular basement membrane between the deposits, accompanied by effacement of the podocyte foot processes (arrowhead).

MANAGEMENT OF MEMBRANOUS LUPUS NEPHRITIS

Class V LN accounts for 5%–10% of all LN cases. Long-term follow-up data show that 10%–30% of patients with Class V LN progress to kidney failure, and the risk of progressive CKD is associated with the severity of proteinuria.

Unlike primary membranous nephropathy, heavy proteinuria in Class V LN does not usually spontaneously remit. Also, heavy proteinuria and NS increase the risk of infections and CV morbidity and predispose patients to thrombosis.

The goals of therapy in patients with LMN include:

- **reduction of proteinuria, especially if the patient has the nephrotic syndrome and is at high risk for complications**
- **prevention of glomerular damage and progression of chronic kidney disease**

GENERAL MEASURES FOR ALL PATIENTS

The **nonimmunosuppressive approaches** are the cornerstone of therapy in patients with subnephrotic range proteinuria.

Proteinuria reduction is an integral part of chronic kidney disease management, as proteinuria is not merely a biomarker of disease activity in patients with LN, but is also a mechanism of chronic kidney disease progression.

Supportive treatments that help control proteinuria include

- **the renin-angiotensin-aldosterone system (RAAS) blockade**
- **blood pressure (BP) control**
- **sodium restriction.**

The benefits **of RAAS blockers** may also include **an immunomodulatory effects**.

Dual RAAS blockade with angiotensin- converting enzyme inhibitors and angiotensin receptor blockers may be more antiproteinuric than either agent alone and can be considered in patients with heavy proteinuria and elevated BP. However, this combination should be used with caution; it can lead to worse renal outcomes in patients with underlying vascular disease

Aldosterone plays an important role in the pathogenesis of renal injury as it promotes fibroblast growthh and vascular remodeling.

Aldosterone antagonists may be used in combination with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for added antiproteinuric effect and BP control.

Antihyperlipidemic therapy should be considered in nephrotic patients, as hyperlipidemia has been linked to podocyte injury, mesangial cell proliferation, and tubulointerstitial disease in nephrotic syndrome and SLE.

Additionally, SLE patients are at a much higher risk for future cardiovascular events compared to the general population.

Hydroxychloroquine — All patients with systemic lupus erythematosus (SLE), regardless of the degree and type of disease activity, should receive treatment with hydroxychloroquine unless contraindicated.

Hydroxychloroquine has been associated with several benefits in patients with SLE, including **improved survival, lower flare rates, and a reduction in organ damage accrual.**

hydroxychloroquine dosed at ≤5 mg/kg/d. 47 Antimalarials have an immunomodulatory effect as they interfere with lysosomal function which is important for T-cell function and antigen presentation.

Antimalarials interfere with toll-like receptor-mediated immune responses, resulting in decreased interferon expression, suppress interleukin-6 levels and decrease inflammatory cytokine production.

Antimalarials also decrease SLE disease activity and have a favorable effect on SLE lipid profile, bone mineral density, and decrease thrombotic events.

IMMUNOSUPPRESSIVE THERAPY

Indications for immunosuppressive therapy

- patients with pure LMN who have nephrotic syndrome

- in the absence of nephrotic syndrome, persistent proteinuria >3.5 g/day despite nonimmunosuppressive therapy;

- a progressive rise in serum creatinine above baseline; or mixed membranous and proliferative lesions on kidney biopsy.

Some experts suggest that patients with **LMN and proteinuria ≥1 g/day (some experts use a threshold of ≥0.5 to 0.7 g/day) without evidence of extensive chronic damage (eg, glomerulosclerosis, interstitial fibrosis and tubular atrophy) on kidney biopsy should receive immunosuppressive therapy.**

The rationale for this approach is that patients **with LMN do not generally experience spontaneous remission**, and this amount of proteinuria increases the risk of progressive kidney damage long term.

Chronic damage on kidney biopsy could suggest that proteinuria is associated more with glomerulosclerosis than with immune complex deposition and **is less likely to respond to immunosuppressive therapy.**

In patients with **proteinuria <1 g/day (some experts use a threshold of <0.5 to 0.7 g/day),** some experts do not treat LMN with immunosuppressive therapy but **rather base the need for immunosuppression on the presence of extrarenal manifestations.**

- **Some experts suggest that all patients with LMN, regardless of the degree of proteinuria, should receive immunosuppressive therapy, given that patients with LMN often do not spontaneously remit.**

All patients with LMN should receive **general supportive therapies** as appropriate (such as renin-angiotensin system inhibition, sodium-glucose cotransporter 2 [SGLT2] inhibition, dietary sodium and protein restriction, and antihypertensive therapy), as well as hydroxychloroquine,

For patients with pure LMN selected for immunosuppression, options for initial therapy include the following:

- **Dual immunosuppressive therapy** – Dual immunosuppressive therapy consists of **glucocorticoids plus one of the following agents:**

  - •Mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS).
  - •Intravenous (IV) cyclophosphamide.
  - •A calcineurin inhibitor (CNI; tacrolimus or cyclosporine).

- **Triple immunosuppressive therapy** – Triple immunosuppressive therapy consists of **glucocorticoids plus one of the following combinations of agents:**
  - •A CNI (voclosporin, tacrolimus, or cyclosporine) plus MMF (or EC-MPS).
  - •Belimumab plus either MMF (or EC-MPS) or cyclophosphamide.

Dual immunosuppressive therapy

Mycophenolate-based regimen :

Specifically,give 0.5 g of MMF twice daily for the first week, then 1 g twice daily for the second week, and thereafter increase the dose as tolerated to between 1 and 1.5 g twice daily. We usually continue MMF at these doses for six months. At six months, the dose may be reduced to 1 g twice daily, which is continued for three to five years and then slowly tapered.

Cyclophosphamide-based regimen :

500 mg every two weeks for a total of six doses; these trials included patients with class III or IV .

At three months, usually switch from cyclophosphamide to MMF (1 g twice daily), which is continued for three to five years.

they did not respond to or could not tolerate MMF therapy, **switch to either a CNI or azathioprine therapy at three months.**

Calcineurin inhibitor-based regimen :

●If **cyclosporine** is used, most would **start dosing at 100 to 200 mg twice daily**. The dose is adjusted to achieve the desired reduction in proteinuria; **the dose is reduced by 25 percent if the serum creatinine increases by 33 to 49 percent or by greater than 0.3 mg/dL on two or more determinations**.

●If **tacrolimus** is used, we usually start **with 1 to 2 mg twice daily** to achieve the desired reduction in proteinuria, reducing the dose as needed if there is an increase in the serum creatinine.

●Some clinicians periodically measure whole blood trough cyclosporine or tacrolimus levels to assess medication adherence and to monitor for supratherapeutic and potentially nephrotoxic levels.

If a clinical response is attained, usually continue **CNI therapy for approximately 6 to 12 months**, **after which time the drug dose is slowly tapered to the lowest effective dose and then eventually discontinued after two to three years**

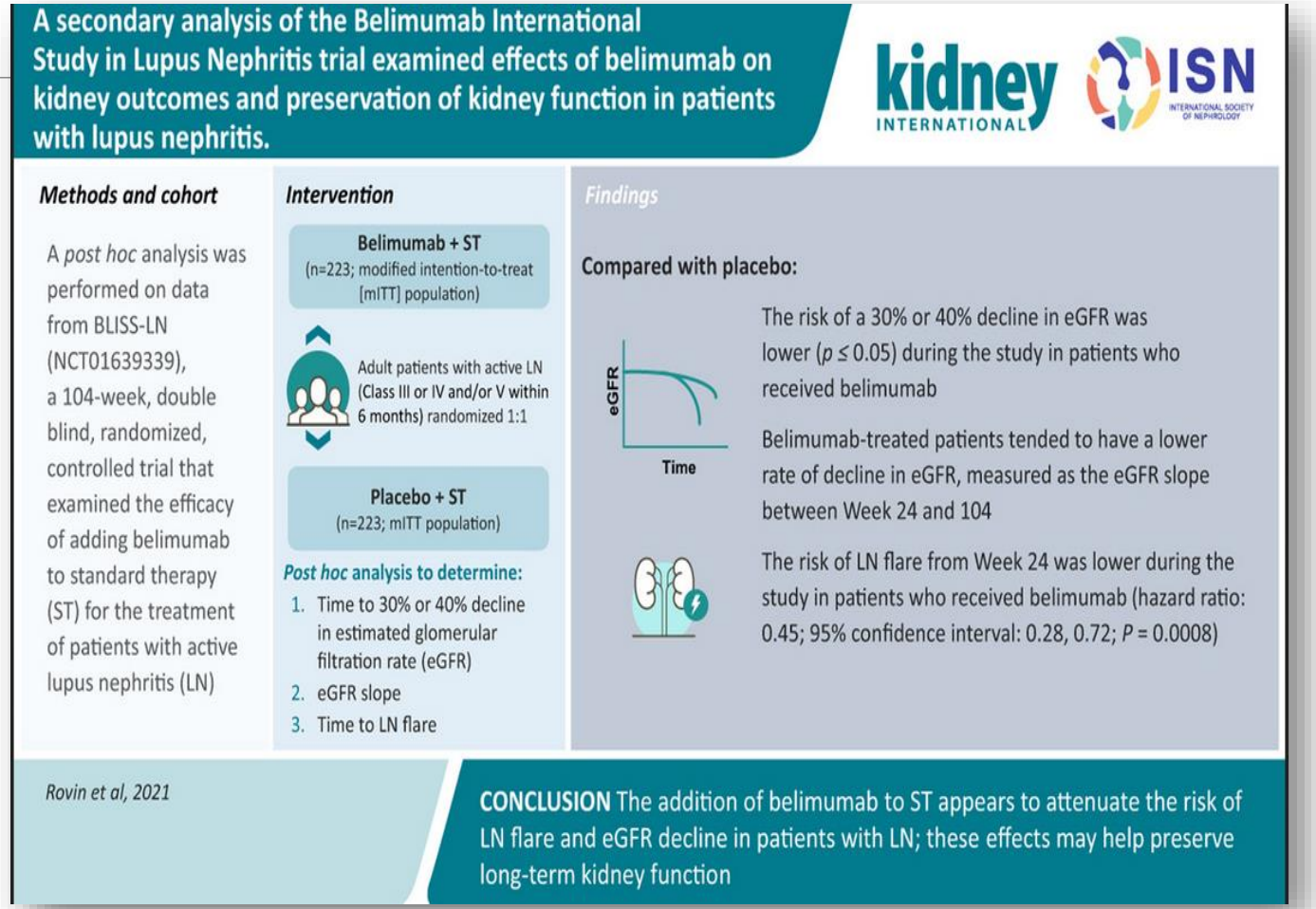
Triple immunosuppressive therapy

Belimumab plus mycophenolate or cyclophosphamide

Belimumab is a human monoclonal antibody that inhibits the soluble form of a B cell survival factor (known as BLyS or BAFF).

Although studies of belimumab in patients with LN used the IV formulation, a subcutaneous form has also been approved for LN. **IV belimumab is administered as 10 mg/kg every two weeks for three doses followed by maintenance dosing every four weeks. Subcutaneous belimumab is initiated as 400 mg once weekly for four doses and then 200 mg once weekly thereafter**.

Belimumab should be used in combination with either a mycophenolate- or cyclophosphamide-based regimen.



Calcineurin inhibitor plus mycophenolate

CNIs used in combination with mycophenolate for LMN include tacrolimus and voclosporin.

voclosporin has the additional benefit of not requiring blood drug concentration monitoring.

Some clinicians have used cyclosporine as an alternative CNI, but evidence to support this approach is more limited.

Tacrolimus and voclosporin have not been directly compared as combination therapy for LMN. **CNIs should be used with caution in patients with preexisting chronic kidney disease and eGFR ≤45 mL/min/1.73 m^2.**

CNIs should be used with a mycophenolate-based regimen when given as part of a combination **regimen.**

●**Tacrolimus** – When tacrolimus is used in combination with mycophenolate, we typically start at **1 to 2 mg orally twice daily and titrate up the dose, depending upon the clinical response** (eg, reduction in proteinuria).

We reduce the dose of tacrolimus if the patient experiences a >30 percent increase in serum creatinine.

Some clinicians target a blood trough tacrolimus concentration of 5 to 7 ng/mL;

other clinicians do not target specific blood levels and monitor tacrolimus concentrations to check for adherence or toxicity. However, levels that correlate with efficacy are not clear.

Clinical Trial > Lancet. 2021 May 29;397(10289):2070-2080. doi: 10.1016/S0140-6736(21)00578-X.
Epub 2021 May 7.

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Voclosporin – Voclosporin is a next-generation CNI that is structurally similar to cyclosporine but is more potent and does **not** require monitoring of drug levels. **Voclosporin is FDA approved for the treatment of LN in combination with mycophenolate and glucocorticoids.**

When voclosporin is used in combination with mycophenolate, it is administered **at 23.7 mg orally twice daily.**

Dose adjustments are required in patients with kidney function impairment or mild to moderate hepatic impairment (Child-Pugh class A or B).

Voclosporin should generally be avoided in patients with a baseline eGFR ≤45 mL/min/1.73 m^2, unless benefit exceeds risk, and those with severe hepatic impairment (Child-Pugh class C)

Cyclosporine – When cyclosporine is used in combination with mycophenolate, we typically **start at 100 to 200 mg orally twice daily and titrate up the dose**, depending on the clinical response (eg, reduction in proteinuria).

We reduce the dose of cyclosporine if the patient experiences a >30 percent increase in serum creatinine.

Some clinicians target a blood cyclosporine concentration of 100 to 150 ng/mL; other clinicians do not target specific blood levels and monitor cyclosporine concentrations to check for adherence or toxicity.

Glucocorticoid dosing and taper

The optimal glucocorticoid regimen for LMN is not certain.

One option for glucocorticoid dosing is suggested by the EULAR/ERA-EDTA guidelines . IV pulse methylprednisolone (250 to 1000 mg given over 30 minutes daily for one to three days) is administered, followed by oral prednisone (or its equivalent) at a dose of ≤0.5 mg/kg/day, then tapered to a dose of less than 5 mg/day by three months and, when possible, withdrawn.

Lower starting doses of glucocorticoids were used in the randomized trial that evaluated the use of voclosporin in combination with MMF and glucocorticoids .

Patients received IV methylprednisolone (500 mg for patients weighing >45 kg and 250 mg for patients weighing <45 kg) once daily on days 1 and 2, followed by a rapid taper of oral prednisone starting on day 3 (starting dose 20 to 25 mg/day, decreased to 2.5 mg/day at week 16, and adjusted thereafter at investigator discretion).

MONITORING RESPONSE TO THERAPY

Follow-up evaluation — After starting initial immunosuppressive therapy, patients are monitored closely to **assess the renal response, control of extrarenal manifestations**, and **potential medication toxicity**.

In the beginning, patients are typically monitored every one to two months, with less frequent monitoring over time if the patient responds and remains stable.

If any significant changes are made to the immunosuppression regimen, we have patients return for a visit in two weeks to assess tolerance; if they are doing well, we return to follow-up visits every one to two months.

Renal response is assessed by following the **serum creatinine** (and estimated glomerular filtration rate [eGFR]), **urine protein excretion** (usually with a spot urine protein-to-creatinine ratio), and **urine sediment examination.**

Other laboratory tests, such as a **complete blood count** and **liver function tests**, are important for medication toxicity monitoring.

Patients treated with standard calcineurin inhibitors (CNIs) should have monitoring of trough drug levels (ie, cyclosporine or tacrolimus levels), while those treated with voclosporin should have their serum creatinine checked monthly.

Patients treated with mycophenolate mofetil (MMF) who do not respond can have MMF levels measured to assess adherence and adequacy of dosing, although this is not commonly performed in practice.

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

RESISTANT DISEASE

Patients with no reduction in proteinuria despite six months of adequate therapy may have resistant disease and require modification of immunosuppressive therapy.

A repeat kidney biopsy may be required to confirm that this is due to persistent LMN or conversion to a different LN class.

The choice of therapy should be individualized based on therapeutic goals, patient preferences, and side effects of therapy.

- **Switching from one dual immunosuppressive regimen to another dual immunosuppressive regimen**

In patients who received initial therapy with glucocorticoids plus a CNI, there are insufficient data to recommend the use of a different CNI (eg, tacrolimus or voclosporin to replace cyclosporine); however, for those who are intolerant of one CNI, a second may be substituted.

●Switching from a dual immunosuppressive regimen to a triple immunosuppressive regimen – As an example, for a patient who has not responded to initial therapy with glucocorticoids plus MMF, a CNI could be added to the MMF.

not add belimumab to MMF for resistant disease based on data suggesting no significant benefit with this combination in patients with LMN .

For a patient who has not responded to initial therapy with glucocorticoids plus cyclophosphamide, not switch to triple therapy by adding belimumab.

- **Switching to rituximab –** In patients who continue to have persistent resistant disease despite one of the above approaches to modifying therapy, rituximab (1 g given on days 1 and 15) is an alternative option.

When switching from one regimen to another, would not restart a new course of glucocorticoids if the patient had already completed the initial course of glucocorticoids.

Some contributors would administer a short course of glucocorticoids (eg, prednisone 20 to 30 mg once daily for two to four weeks), followed by a taper.

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative recommended treatment regimen when there is persistent active disease
5	Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible

RELAPSING DISEASE

Patients who have an **initial response** to therapy but **then develop worsening proteinuria, a new active urinary sediment, or worsening kidney function may have relapsing disease.** A repeat biopsy often is required to confirm that this scenario is due to a relapse of LMN or conversion to a different LN class.

For most patients who develop a relapse of LMN, we suggest reinstitution of the same initial therapy used to achieve the original response. However, it is also reasonable to modify the initial therapy regimen (eg, adding a CNI, belimumab, or rituximab to a mycophenolate-based regimen) or switch to an alternative immunosuppressive regimen.

The choice of therapy should be individualized based on patient preferences and adverse effects of therapy. In patients who have received multiple prior courses of cyclophosphamide for whom there is concern for cumulative toxicity or risk of infertility, it may be preferable to use a mycophenolate- or CNI-based regimen.

There are no high-quality data to guide the optimal treatment of relapsing LMN.

TREATMENT-RELATED TOXICITY AND PROPHYLAXIS

Immunosuppressive therapy with cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors (CNIs), and/or high-dose glucocorticoids has both **infectious and noninfectious toxicities that warrant additional prophylactic measures.**

- Vaccinations for all patients – Patients receiving immunosuppressive therapy for LN are at increased risk for infection and should receive age-appropriate vaccinations for immunosuppressed individuals. These are discussed separately.

Prophylaxis for specific immunosuppressive agents

Glucocorticoids – Patients receiving systemic glucocorticoids are at risk for several adverse effects on multiple organ systems

Patients receiving a glucocorticoid dose equivalent to ≥20 mg of prednisone daily for one month or longer should receive prophylaxis for Pneumocystis jirovecii (PJP) pneumonia.

•**Cyclophosphamide** – Cyclophosphamide is associated with a variety of toxicities, including **hematologic toxicity, infection, gonadal toxicity, malignancy, and bladder toxicity.**

Patients receiving cyclophosphamide, **especially when combined with glucocorticoids**, should receive **prophylaxis for PJP pneumonia.**

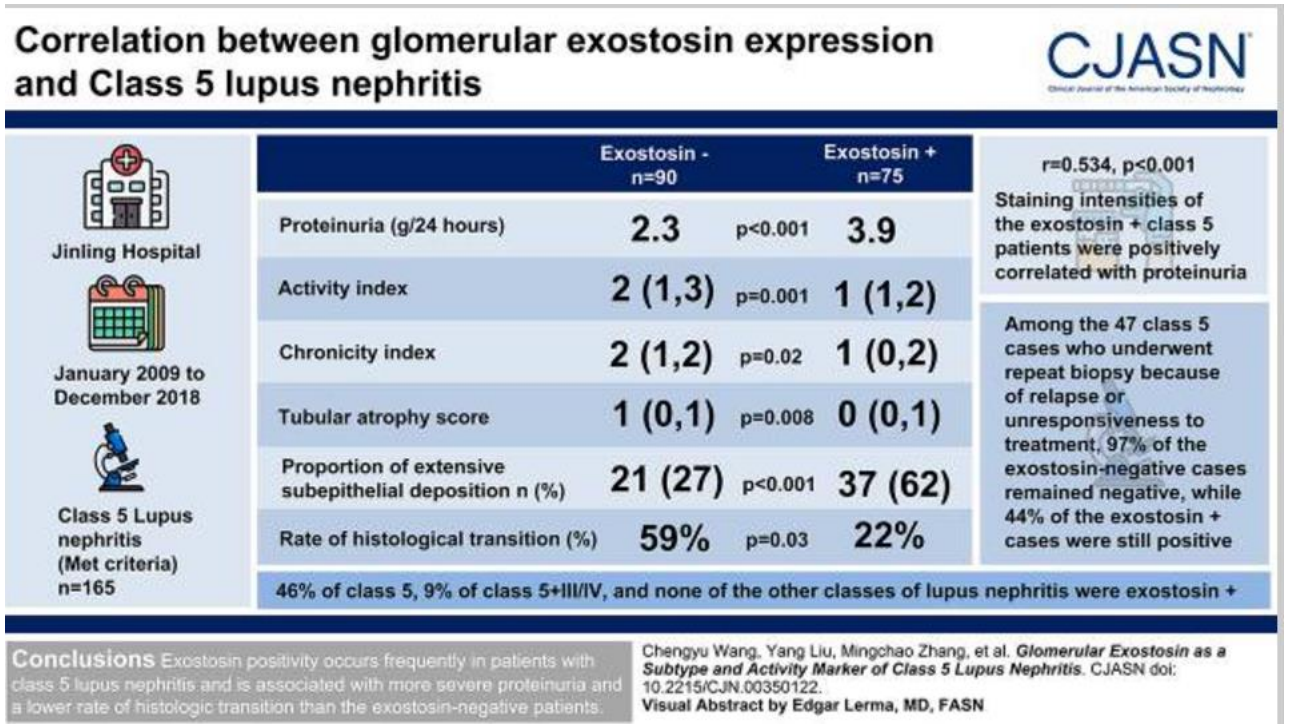
PROGNOSIS

The reported kidney survival rates are generally favorable among patients with LMN . Among patients with pure LMN, 10-year kidney survival rates range from 72 to 98 percent .

However, patients who have concurrent class III or IV lesions have lower long-term kidney survival compared with those who have pure LMN .

Other contributing factors to variable outcomes include **differences in patient populations and in immunosuppressive therapies that may be used for extrarenal indications**

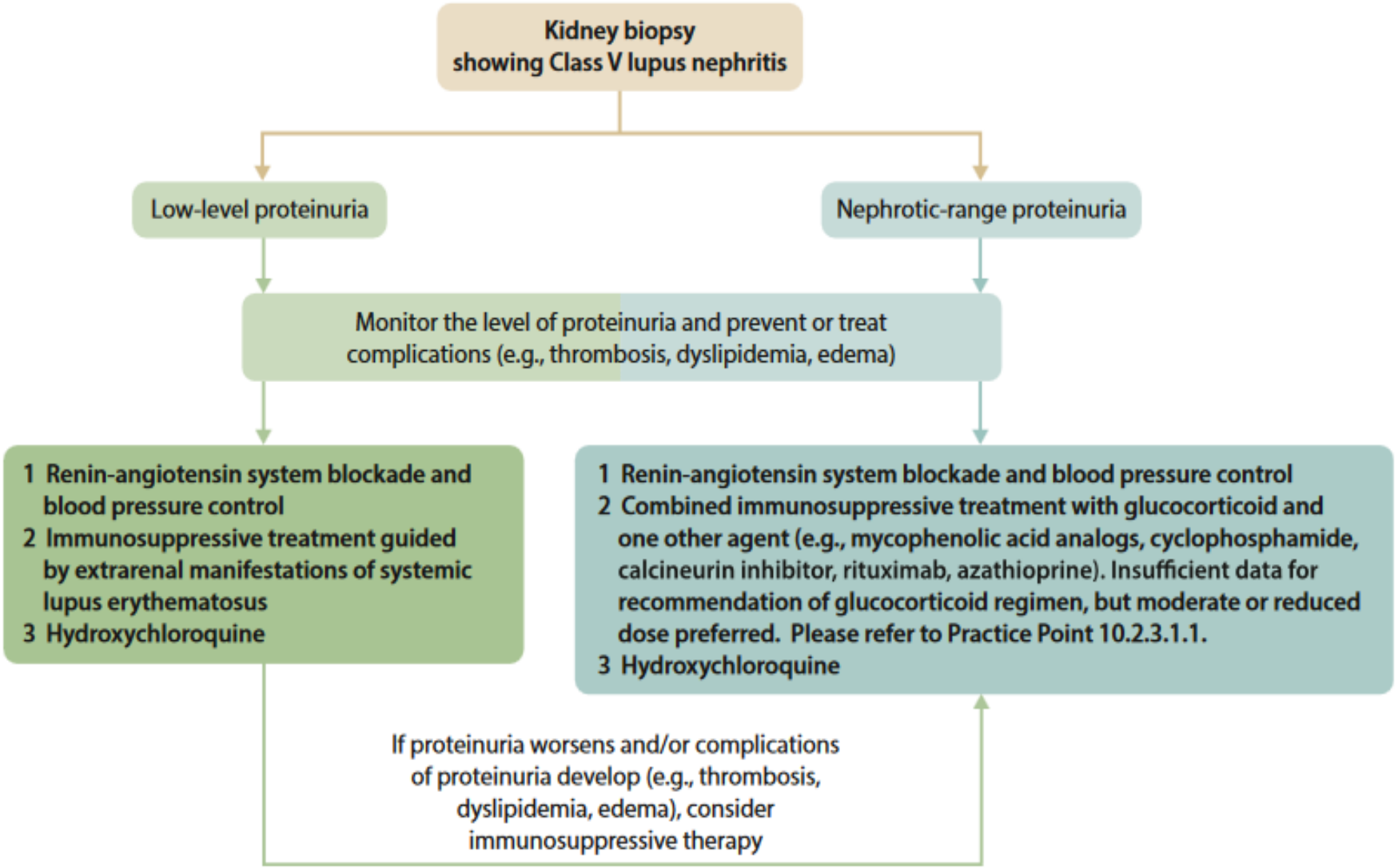
xostosin-1 and -2 (EXT1/EXT2) have been identified as potential disease biomarkers in a proportion of patients with LMN



In a study of 374 patients with biopsy-proven LMN, of whom approximately one-third were positive for EXT1/EXT2, **those who were EXT1/EXT2 positive were younger, had lower serum creatinine levels, and had fewer chronic features** (ie, glomerulosclerosis, interstitial fibrosis and tubular atrophy) on kidney biopsy .

Compared with patients who were EXT1/EXT2 positive, those who were EXT1/EXT2 negative progressed to ESKD more quickly and more frequently (19 versus 3 percent).

However, a subsequent observational study found no significant difference in rates of kidney failure or estimated glomerular filtration rate (eGFR) decrease of >50 percent between EXT1/EXT2-positive and EXT1/EXT2-negative patients with LMN


Kidney biopsy showing Class V lupus nephritis
Low-level proteinuria
Nephrotic-range proteinuria
Monitor the level of proteinuria and prevent or treat complications (e.g., thrombosis, dyslipidemia, edema)
1 Renin-angiotensin system blockade and blood pressure control
2 Immunosuppressive treatment guided by extrarenal manifestations of systemic lupus erythematosus
3 Hydroxychloroquine
1 Renin-angiotensin system blockade and blood pressure control
2 Combined immunosuppressive treatment with glucocorticoid and one other agent (e.g., mycophenolic acid analogs, cyclophosphamide, calcineurin inhibitor, rituximab, azathioprine). Insufficient data for recommendation of glucocorticoid regimen, but moderate or reduced dose preferred. Please refer to Practice Point 10.2.3.1.1.
3 Hydroxychloroquine
If proteinuria worsens and/or complications of proteinuria develop (e.g., thrombosis, dyslipidemia, edema), consider immunosuppressive therapy