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About the Author

Konstantinos Tselios, MD, PhD

Dr. Tselios is an Assistant Professor of Medicine with the Division of Rheumatology at McMaster University since 2021. He completed his basic training and PhD in Greece and came to Canada in 2014 where he worked as a post-doctoral fellow with the University of Toronto Lupus Clinic. His main clinical and research interest is the field of autoimmunity and systemic lupus erythematosus, particularly the cardiovascular complications of the disease. He has published more than 70 peer-reviewed articles and book chapters. He is currently developing the McMaster Lupus Clinic and Lupus Ontario/Anne Matheson Lupus Biobank in Hamilton.

Affiliations: McMaster Lupus Clinic, Division of Rheumatology, Department of Medicine, McMaster University

Management of Adult Patients with Lupus Nephritis: Therapeutic Algorithm Based on the Current Treatment Guidelines

Konstantinos Tselios, MD, PhD

Introduction

Lupus nephritis (LN) is one of the most significant manifestations of systemic lupus erythematosus (SLE) affecting approximately 35–40% of patients in large cohort studies.[1] It is usually diagnosed in the early phases of the disease; among those with LN, approximately 80% are diagnosed at or shortly after disease onset. LN is characterized by histological and clinical heterogeneity and substantially affects survival. A meta-analysis of 18,309 LN patients reported a 10-year risk for the development of end-stage kidney disease (ESKD) of nearly 17% overall and 33% among those with LN class IV (diffuse proliferative form).[2] Early detection and timely management are essential for optimizing outcomes. Given that LN patients are often asymptomatic, it is recommended that all lupus patients, particularly early in the disease course, undergo routine screening every 3–6 months.[3] This includes assessment of proteinuria with urinary protein- or albumin-to-creatinine ratio (and 24 hour urine protein if indicated), urinary sediment and serum creatinine, regardless of disease activity.[3] If abnormal findings that cannot be explained by alternative causes are detected (proteinuria ≥500 mg/day, active urinary sediment with acanthocytes ≥5% or red blood cell casts or white blood cell casts, increased serum creatinine) a renal biopsy should be performed, as it remains the gold standard for confirming the diagnosis, management planning, and informing the prognosis.

Herein, we present a step-by step approach to the current management of adult LN as recommended by the 2024 American College of Rheumatology (ACR),[4] the 2025 updated European Alliance of Associations for Rheumatology (EULAR),[5,6] as well as the 2024 KDIGO (Kidney

Disease: Improving Global Outcomes)[7] guidelines. New treatment options that will be available in the near future are also discussed briefly.

Should emphasize that the focus is on adult LN approach. The ACR guidelines also discuss children, so I think it should be acknowledged that the focus here is for adults.

If the author is not going to talk about the KDIGO guidelines (which are more recent than the EULAR guidelines), they should be at least acknowledged early on and perhaps just mention some of the differences between ACR/KDIGO as readers it's been a point of debate and discussion at multiple lupus meetings.

Induction Therapy for LN Class III and IV (With or Without V)

Management of LN should begin promptly (even in anticipation of the kidney biopsy if there is no alternative explanation) and based on aggressive immunomodulatory therapy with glucocorticoids and immunosuppressives as well as adjuvant therapies. All guideline sets (2024 ACR, 2025 EULAR, 2024 KDIGO) recommend the use of antimalarials, mainly hydroxychloroquine, in all patients with LN unless contraindicated.[4-7] Hydroxychloroquine has recently been characterized as a disease-modifying drug due to its ability to prevent disease flares, decrease the risk for thrombosis, delay damage accrual, and improve survival.[8]

The use of intravenous methylprednisolone pulses as an initial approach is also recommended by all guideline sets.[4-7] The goal is to achieve rapid suppression of the autoimmune inflammation at the tissue level and allow for the subsequent transition to lower doses of oral prednisone. Dosing strategies are not standardized and depend on the severity of the disease as well as extra-renal manifestations. Most commonly, intravenous methylprednisolone is administered in pulses of 250–1000 mg daily for up to three consecutive days.

Oral glucocorticoids should be administered following the initial intravenous methylprednisolone pulses. In randomized controlled trials (RCTs), oral glucocorticoids have historically been used in various doses (up to 1 mg/kg body weight [BW] or 80 mg/day of prednisone equivalent). However, a recent pooled analysis of nine RCTs showed that low prednisone doses (up to 0.5 mg/kg BW) are equally effective as higher doses (up to 1 mg/kg BW) in achieving overall renal response (defined as combined complete and partial renal responses at 12 months).[9] Moreover, patients who had received lower prednisone doses experienced significantly fewer serious adverse events and serious infections. Consequently, both the 2024 ACR and 2025 EULAR guidelines recommend an initial prednisone dose of ≤0.5 mg/kg BW (maximum daily dose of 40 mg/day) with a tapering schedule targeting ≤5 mg/day at 6 months (ACR) or ≤7.5 mg/day at 3–6 months (EULAR).[4-6] The 2024 KDIGO guidelines suggest 3 different schemes for oral glucocorticoids according to initial disease severity (high-dose scheme with a maximum starting dose of 80 mg/day, a moderate-dose scheme starting at 50 mg/day and a reduced-dose scheme starting at 40 mg/day).[7] Accordingly, the goal is to reduce the daily prednisone dose to ≤5 mg by week 24 from treatment initiation (2.5 mg/day for the reduced-dose scheme). In general, all guideline sets agree that cumulative glucocorticoid exposure should be minimized and a daily prednisone dose of 5 mg at 6 months should be considered as a treatment goal.[4-7]

Immunosuppressive therapy is considered the cornerstone of LN management and should be initiated concomitantly with glucocorticoids. All guidelines strongly recommend the use of mycophenolic acid (MPA), its prodrug mycophenolate mofetil (MMF), or cyclophosphamide (CYC), which are considered equivalent regarding efficacy based on findings from several randomized controlled trials.[10] A recent meta-analysis of 1,989 LN patients demonstrated that MPA/MMF may offer a slight advantage in overall efficacy and substantially less ovarian toxicity compared to CYC.[11] The favourable safety profile of MPA/MMF renders them more appropriate for use in daily practice, particularly given the demographic characteristics of the majority of LN patients (young women). Reflecting this, the ACR conditionally recommends MPA over CYC.[4] The target dose for MPA is 1.44–2.16 g/day (equivalent to 2–3 g/day for MMF). In contrast, CYC is administered in intermittent pulses (preferably 500 mg every 2 weeks for six pulses, Euro-Lupus protocol, or 0.5–0.75 g/m^2 monthly for 6 months in the presence of adverse clinical or histologic features, NIH protocol). In general, lower CYC doses (Euro-Lupus protocol) are preferred (and recommended by the ACR)[4] to prevent long-term side effects such as infertility and malignancies. CYC may be more appropriate in patients who have difficulty adhering or being

intolerant to MPA/MMF or in cases of rapidly progressing glomerulonephritis (2024 ACR).[4]

The combination of glucocorticoids with either MPA/MMF or CYC is considered the minimum standard of care (SoC) for LN. However, given that complete renal remission (CRR) with these regimens is achieved in less than one-third of patients,[12] all recent guidelines recommend triple therapy with the addition of calcineurin inhibitors (CNIs) or B-cell targeted therapies (belimumab, obinutuzumab) as part of the SoC.[4-7]

CNIs have been extensively used in the management of other immune-mediated nephropathies and for preventing transplant rejection. In LN, tacrolimus (TAC) in combination with MMF (in doses of 1 g/day) demonstrated superior efficacy over CYC in Chinese LN patients, particularly those with class IV and V LN, achieving a complete renal response rate of 45.9% versus 25.6%, respectively, at 24 weeks.[13] This approach, termed multi-targeted therapy, emphasized the multiple pathogenetic pathways that participate in LN pathogenesis. In the AURORA-1 trial, voclosporin (plus SoC) performed substantially better versus SoC alone, achieving a complete renal response rate of 41% versus 23% at 52 weeks.[14] Voclosporin is a cyclosporine analog with enhanced metabolic stability and favorable safety profile. Notably, approximately 90% of patients experienced a 50% reduction of their baseline proteinuria within 7–8 months. Concerns about long-term nephrotoxicity were not verified in the AURORA 2 trial, which showed no reduction in estimated Glomerular Filtration Rate (eGFR) after 30 months of voclosporin treatment.[15] CNIs are recommended in combination with MPA/MMF primarily for patients with relatively preserved kidney function and nephrotic range proteinuria (>3 g/24 hours), likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPA/MMF or are unfit for or will not use CYC-based regimens.[4,7] The maximum dose for TAC is 4 mg/day (divided in two doses), while voclosporin is dosed at 23.7 mg twice daily. It should be mentioned that voclosporin is currently not available in Canada. New-onset hypertension, hyperglycemia, and nephrotoxicity as well as the need for drug level monitoring should also be considered with CNIs.

B cells play a fundamental role in SLE pathogenesis, and targeting them with monoclonal antibodies has led to significant improvements in disease activity. Despite the failure of the LUNAR trial to meet its primary endpoint, rituximab (a type 1 anti-CD-20 antibody) has shown favourable effects in LN, particularly when complete B-cell depletion is achieved.[16] Condon et al. applied a “no oral steroid regime” using rituximab at a dose of 1000 mg on days 1 and 15 with 500 mg of concomitant methylprednisolone followed by MMF, showed substantial efficacy in LN.[17] Belimumab, a B lymphocyte stimulator (BLyS) inhibitor, in combination with SoC demonstrated superior efficacy in the BLISS-LN trial at 104 weeks, achieving a complete renal response rate of 30% versus 20% with placebo plus SoC. This led to belimumab becoming the first biologic to be approved for treating LN.[18] Belimumab is recommended in combination with MPA/MMF or CYC for LN class III or IV, particularly in patients where extra-renal manifestations are prevalent[4-6] or with repeated kidney flares or at high risk for progression to kidney failure due to severe chronic kidney disease.[7] Most recently, obinutuzumab, a type 2 anti-CD20 antibody, demonstrated improved outcomes in the REGENCY trial when added to SoC therapy (glucocorticoids and MMF), achieving a complete renal response rate of 46.4% compared to 33.1% of placebo plus SoC at week 76.[19] Obinutuzumab showed particularly enhanced efficacy in patients with nephrotic-range proteinuria, active lupus serology (abnormal anti-dsDNA and/or low complement C3/C4 levels), and in newly diagnosed patients. Obinutuzumab has been approved by the FDA; it has been included as an alternate therapy for addition to SoC in the new 2025 EULAR guidelines.[6]

Induction Therapy for Pure LN Class V

Management of pure membranous LN (class V) should be guided by the level of initial proteinuria. In patients with proteinuria ≥1 g/day, the 2024 ACR guidelines recommend triple therapy with glucocorticoids, MPA/MMF and CNIs.[4] Regarding glucocorticoids, methylprednisolone pulses should still be applied but, in general, the oral prednisone doses should be lower (maximum of 40 mg/day per ACR or 50 mg/day per KDIGO).[4,7] If ineffective, CYC for less than 6 months or B-cell targeted therapies may be considered.

In patients with milder proteinuria (<1 g/day), the 2024 ACR guidelines recommend treatment with glucocorticoids (low oral doses) plus an immunosuppressive (MPA/MMF or CNI or azathioprine) and close monitoring of proteinuria.[4] On the contrary, the 2024 KDIGO guidelines state that immunosuppressive treatment should

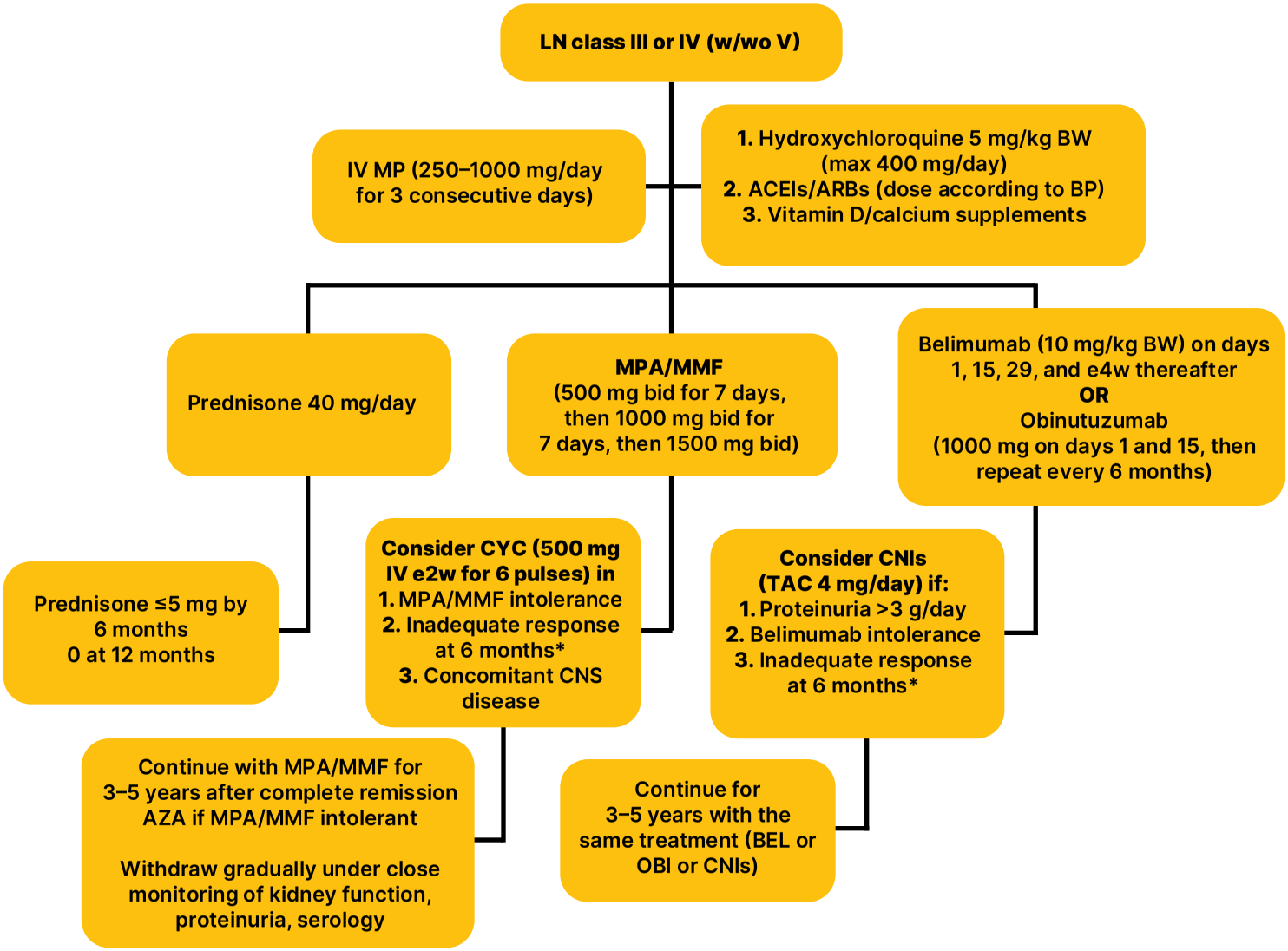

Figure 1. Therapeutic algorithm for LN class III and IV (with or without V); *courtesy of Konstantinos Tselios, MD, PhD.*

*No partial renal response (50% improvement in proteinuria from baseline and stable renal function).

Obinutuzumab was superior to placebo and SoC in the phase III Regency trial.
Voclosporin is not available in Canada and not mentioned in this figure.

Abbreviations: ACEIs: angiotensin-converting enzyme inhibitors; **ARBs:** angiotensin receptor blockers; **AZA:** azathioprine; **BEL:** belimumab; **CNIs:** calcineurin inhibitors; **CNS:** central nervous system; **CYC:** cyclophosphamide; **LN:** lupus nephritis; **MMF:** mycophenolate mofetil; **MP:** methylprednisolone; **MPA:** mycophenolic acid; **OBI:** Obinutuzumab; **TAC:** tacrolimus.

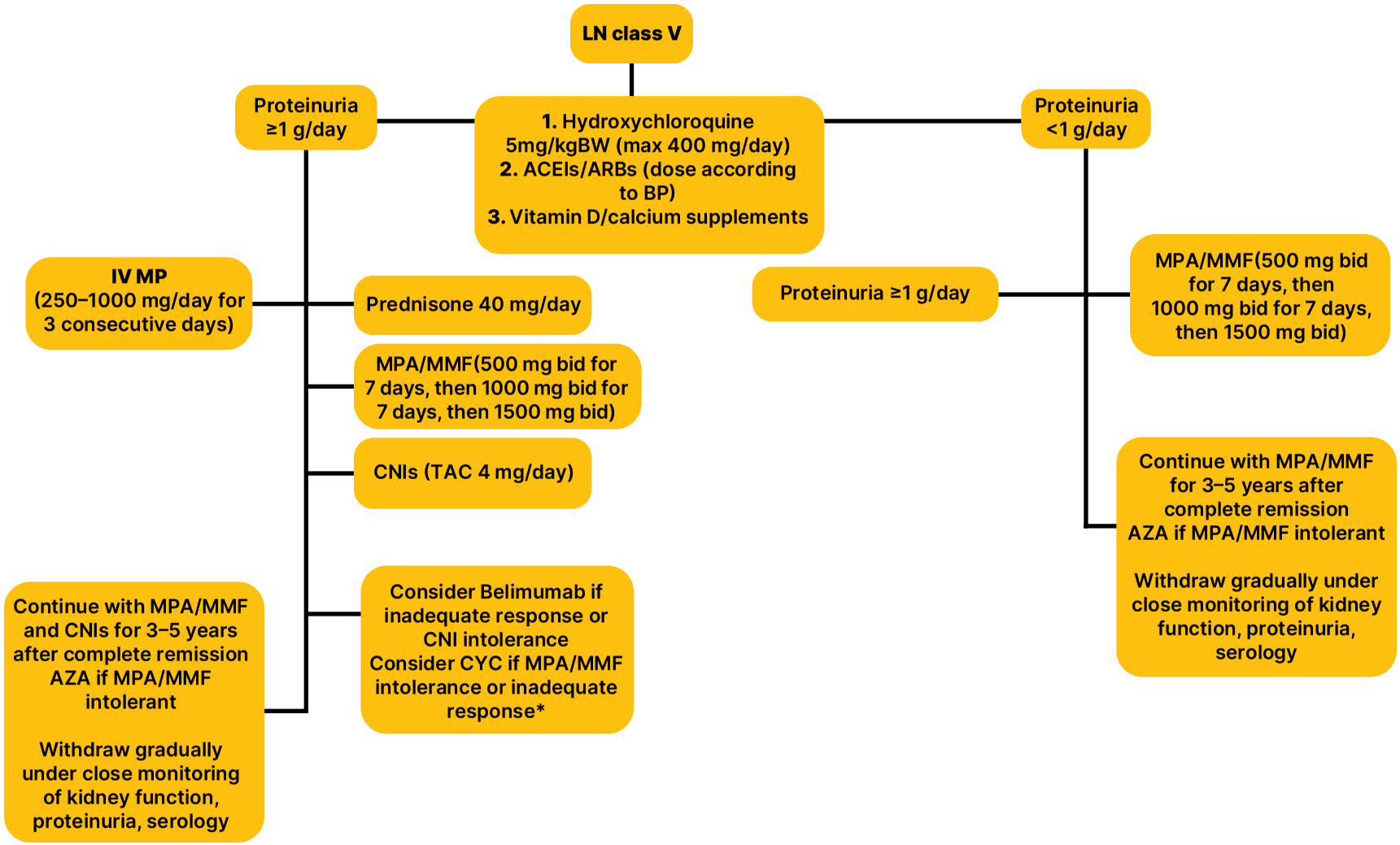

Figure 2. Therapeutic algorithm for LN class V; *courtesy of Konstantinos Tselios, MD, PhD.*

*No partial renal response (50% improvement in proteinuria from baseline and stable renal function).

Voclosporin is not available in Canada and not mentioned in this figure.

Abbreviations: ACEIs: angiotensin-converting enzyme inhibitors; **ARBs:** angiotensin receptor blockers; **AZA:** azathioprine; **bid:** twice a day; **CNIs:** calcineurin inhibitors; **CYC:** cyclophosphamide; **LN:** lupus nephritis; **MMF:** mycophenolate mofetil; **MP:** methylprednisolone; **MPA:** mycophenolic acid; **TAC:** tacrolimus.

be based on the extrarenal SLE manifestations while proteinuria should be treated with renin-angiotensin system blockade and blood pressure control.[7]

The EULAR guidelines recommend triple therapy with glucocorticoids, MPA/MMF and CNIs (especially tacrolimus) in cases with nephrotic range proteinuria; CYC can be used as an alternative to MPA/MMF.[5]

Adjuvant Therapies for LN

Adjuvant, non-immunosuppressive, therapies are fundamental in achieving treatment goals in LN. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are conditionally recommended in all LN patients (unless contraindicated) for managing any increase in proteinuria, even at levels <0.5 g/day.[4-7] These recommendations are extrapolated from other proteinuric nephropathies, as their efficacy in pure LN populations has not been confirmed. Nevertheless, they remain important for blood pressure control in LN and are useful in patients where proteinuria is attributed to chronic nephron damage. Sodium-glucose cotransporter 2 inhibitors (SGLT-2) have also demonstrated nephroprotective properties in other kidney diseases and may reduce the risk for chronic and ESKD in patients with LN with concomitant diabetes.[20] Their use might be considered in cases of chronic LN with diabetes or heart failure or chronic kidney disease.[4,7] Other nephroprotective strategies (optimization of blood pressure, low sodium intake <2 g/day and avoidance of high protein diet if eGFR<60 ml/min/1.73m^2) are also recommended by all guidelines.

Other measures to minimize the risk of complications and optimize outcomes include considerations for cardiovascular health (management of hypertension, dyslipidemia, diabetes, smoking cessation, BMI optimization among others), bone health (vitamin D and calcium supplementation and fracture risk assessment with appropriate management), infection control (screening for chronic infections, appropriate vaccinations and consideration of prophylactic therapy for Pneumocystis jirovecii) and reproductive health (contraception methods, gonadotropin releasing hormone agonists in females treated with CYC among others).

Goals of Treatment in LN

Achieving CRR, defined as proteinuria <0.5 g/day and stable kidney function (eGFR±10–15% of the baseline value), is considered the optimal goal of LN management. While there is broad consensus on the importance of stable eGFR, RCTs have used a more lenient threshold for proteinuria, for example, the BLISS-LN trial accepted levels of up to 700 mg/day.[18] The timing of CRR achievement is of paramount importance, as achieving CRR by 12 months offers substantially better long-term prognosis, extending over 20 years, than CRR achieved at 24 or 36 months.[21] The minimum goal of treatment is achieving partial renal remission by 6 months, defined as a reduction in proteinuria of >50% without a significant decrease in renal function (eGFR±10–15% of baseline).[4-7] Moreover, all guidelines now incorporate oral glucocorticoid tapering into treatment goals, recommending a dose of ≤5 mg/day at 6 months[4-6] or even lower (2.5 mg/day if the KDIGO reduced-dose scheme was employed).[7]

What to Do if Goals are Not Achieved?

In cases of refractory disease, medication dose and patient adherence should be assessed regularly as an important first step. In patients who were treated with dual therapy (i.e., glucocorticoids and MPA/MMF or CYC), escalation to triple therapy with the addition of belimumab[4-7] or obinutuzumab[6] or CNIs[4-7] is recommended. In patients who were initially treated with triple therapy, alternate triple therapy should be employed (i.e., belimumab instead of CNIs or vice versa) or addition of an anti-CD20 agent (rituximab, obinutuzumab) on MPA/MMF or low dose CYC.[4] In patients who have failed two standard therapy courses, addition of an anti-CD20 agent or quadruple therapy (glucocorticoids plus MPA/MMF plus belimumab plus CNIs) or investigational therapy should be considered.[4]

In cases of disease relapse after achieving remission, the 2024 KDIGO guidelines recommend the same therapy that initially achieved remission or an alternate recommended therapy.[7]

In patients who develop ESKD, both the 2024 ACR and 2024 KDIGO guidelines recommend pre-emptive kidney transplantation over hemodialysis as this is related to substantially improved survival.[4,7] Clinical and serological

quiescence are not a requirement to proceed with transplantation (as long as there is no other major organ involvement) according to the ACR.[4] In cases where kidney transplant is not an option, hemodialysis or peritoneal dialysis should be initiated in collaboration with Nephrology.[4,7]

Maintenance Therapy

Management of LN should be long-term and aim to reduce the risk of subsequent disease flares that can lead to nephron loss and eventually to chronic kidney disease. All guidelines strongly recommend continuing maintenance therapy with the same immunosuppressive regimen used to achieve CRR, typically MPA/MMF following induction therapy with CYC, for at least 3–5 years (if not more).[4-7] Patients who received more than 3 years of immunosuppressive treatment had substantially better outcomes over a 20-year period compared to those with shorter treatment durations.[21] Based on findings from repeated kidney biopsies, De Rosa et al. showed that LN patients in proteinuric complete remission for 12 months may still have active disease at the tissue level.[22] These patients were at risk for disease flares following the discontinuation of immunosuppressive therapy, highlighting the need for biomarkers that could better characterize the state of LN beyond proteinuria alone. Multiple urinary biomarkers have been identified that may help to predict ongoing histologic activity and may eliminate the need for repeat kidney biopsies in the future.[23]

Withdrawal of immunosuppressive therapy after prolonged complete remission should be individualized and carried out gradually under close clinical and laboratory monitoring. This includes assessments of kidney function, proteinuria, and lupus serology markers (anti-dsDNA antibodies and complement levels [C3/C4]). In the WIN-Lupus trial, maintenance of immunosuppressive therapy for more than 3 years did not demonstrate statistically superior results compared to discontinuation (relapse rates: 12.5% versus 27.3%, difference 14.8%, 95% confidence interval -1.9–31.5).[24] However, the small number of patients did not allow for sound conclusions. Notably, patients who discontinued immunosuppressive therapy developed a significantly higher rate of non-nephritic lupus flares.

Future Prospects: CAR T-Cell Therapy for LN

Chimeric antigen receptor T-cell (CAR T) therapy was first administered to a patient with refractory LN in 2021.[25] The patient had received all available treatments for her LN to no avail; however, a rapid and profound clinical and serologic response was documented shortly after the administration of CD-19 engineered T cells, and has remained in drug-free remission ever since. CAR T-cell therapy has now been successfully administered to more than 50 patients with refractory SLE worldwide, the majority of them with concomitant LN.[26] This approach has also been employed in children and adolescents with LN.[26] Currently, over 60 RCTs in early phases are recruiting patients with systemic autoimmune diseases to evaluate CAR T-cell therapy. The mechanistic basis involves targeting of B cells through molecules such as CD19 or B-cell maturation antigen (BCMA) (or both) that are expressed on the surface of B cells in different stages of their functional maturation. Compared to biologics like rituximab, CAR T-cells have the advantage of deeper and sustained depletion of the B cells given their persistence in the peripheral blood as well as their capacity for tissue penetration and eradication of the B cells that reside in germinal centres within the affected organs. However, the cost of this therapy remains an obstacle to its wide adoption in lupus treatment.

Conclusions

LN treatment should begin promptly and target complete renal remission within 12 months from initiation. All patients should be treated with hydroxychloroquine and glucocorticoids (initially with intravenous pulses and subsequently orally) and aim at a prednisone dose of ≤5 mg/day by 6 months. Immunosuppressive agents (MPA/MMF or low-dose CYC), and biologics (belimumab, obinutuzumab) or CNIs (TAC, voclosporin) should be added for class III–IV and pure class V with proteinuria ≥1 g/day. Early initiation of adjuvant treatments, including ACEIs/ARBs, is recommended. Maintenance therapy with the same immunosuppressive regimen should be continued for at least 3–5 years after remission.

Corresponding Author

Konstantinos Tselios, MD, PhD
Email: tseliosk@mcmaster.ca

Financial Disclosures

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