

Choosing the Right Treatment in Patients with Lupus Nephritis

Juan Manuel Mejia Vilet,¹ Zhi-Hong Liu,² and Tak Mao Chan ³

CJASN 17: 1399–1402, 2022. doi: <https://doi.org/10.2215/CJN.04120422>

Introduction

Severe lupus nephritis is an important cause of CKD. Patient heterogeneity in disease manifestations, risk profile, and response to therapies present significant challenges in clinical management.

Case Presentation

The case is a 33-year-old woman who has relapsed lupus nephritis and heavy proteinuria. She first presented 2 years ago with microscopic hematuria, urine protein-creatinine ratio of 0.9 g/g, serum creatinine of 2.1 mg/dl, eGFR=31 ml/min per 1.73 m², albumin of 33 g/L, high anti-dsDNA, and low C3, with no extra-renal lupus manifestation. Kidney biopsy showed class 4 lupus nephritis with a modified National Institutes of Health (NIH) activity score of ten and a chronicity score of one. She responded well to treatment with methylprednisolone (0.5 g/d intravenously for 2 days) followed by oral prednisolone, the Euro-Lupus cyclophosphamide regimen, and then mycophenolate, with complete resolution of proteinuria and hematuria and improved serum creatinine and eGFR to 1.2 mg/dl and 61 ml/min per 1.73 m², respectively. Anti-dsDNA level decreased but remained low-titer positive, and C3 remained subnormal. Prednisolone was tapered off after 20 months. She is taking mycophenolate mofetil 500 mg twice daily and hydroxychloroquine 200 mg daily and has noticed ankle swelling for 2 weeks. Anti-dsDNA has increased, and C3 has decreased. Urine protein-creatinine ratio and serum creatinine have increased to 4.6 g/g and 3.3 mg/dl, respectively, with eGFR=18 ml/min per 1.73 m². Repeat kidney biopsy shows classes 4 and 5 lupus nephritis with a modified NIH activity score of nine and a chronicity score of five. How should one treat the relapsed lupus nephritis?

Discussion

General Comments on Lupus Nephritis Management and Personalized Considerations

Lupus nephritis is characterized by a relapsing clinical course, and many patients present at an early age. Patient management should incorporate a long-term

perspective on the outcomes targeted and a global risk assessment that takes into consideration distinct characteristics and comorbidities. Prior drug exposure and disease course inform the choice of fitting immune-interventional therapies with the optimal benefit-risk ratio. Adjunctive therapies and lifestyle modifications minimize complications and damage accrual related to disease or treatment, as well as disruptions to normal activities and quality of life. Examples include hydroxychloroquine and controlling cardiovascular risk factors. CKD of variable severity is common; therefore, renoprotective measures (in particular, treatment of hypertension) are important for kidney and cardiovascular protection.

The diagnosis of active class 3/4±5 lupus nephritis can be obvious when there is kidney deterioration accompanied by active serology. Nevertheless, kidney biopsy provides important information that guides management, including activity versus chronicity, the latter affecting prognosis and susceptibility to treatment toxicities, and concomitant abnormalities, such as thrombotic microangiopathy or membranous feature, which have implications on the natural history and choice of therapy. The immediate objective is rapid control of immune-mediated inflammation for the reversal of AKI and nephron preservation. This is achieved with combined immunosuppressive regimens initially at high dosage. Continuation of immunosuppression, with dosage tapering, consolidates treatment response and prevents relapse; otherwise, further attrition of nephron mass portends reduced kidney survival. The relapsing course, chronic kidney impairment, and concomitant classes 4 and 5 features with heavy proteinuria are salient characteristics of this patient that inform management decisions.

How to Select Initial and Maintenance Immunosuppressive Regimens

Combined immunosuppression with glucocorticoid and either mycophenolate or cyclophosphamide is the recommended initial therapy in various guidelines on the basis of proven efficacy and long-term clinical experience (1,2). The dose, rate of tapering, and duration of glucocorticoid vary considerably between clinicians and are largely opinion based. As shown in recent

¹Departamento de Nefrología y Metabolismo Mineral, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

²National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, People's Republic of China

³Department of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China

Correspondence:

Prof. Tak Mao Chan, Room PB408, 4th Floor Professorial Block, University of Hong Kong, Department of Medicine, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Email: dtmchan@hku.hk

clinical trials, there is a move toward targeting a lower glucocorticoid exposure. Typical regimens often start with methylprednisolone at 0.5–1.0 g/d intravenously for 2–3 days followed by daily oral glucocorticoid with progressive tapering. Mycophenolate mofetil (or mycophenolic acid sodium at an equivalent dose) at around 2 g/d in divided doses in Asian or Caucasian patients or up to 3 g/d in others is used for 6–12 months followed by gradual tapering. Measurement of mycophenolic acid blood level may be useful in select patients who show unsatisfactory treatment response or treatment-associated adverse effects. Reduced-dose cyclophosphamide (500 mg intravenously fortnightly for 3 months; the Euro-Lupus regimen) is recommended, although the modified NIH regimen at 0.5–1 g/m² intravenously monthly for up to 6 months can be considered in patients with low cumulative drug exposure and severe disease, such as those with extensive crescents, especially in “high-risk” groups (for example, patients of African descent). Potential adverse effects such as marrow or gonadal toxicity, alopecia, and malignancy predisposition, and also the inconvenience and cost of intravenous infusions, are the disadvantages of cyclophosphamide. The choice between mycophenolate and cyclophosphamide also takes into consideration the response and tolerance to treatments in previous flares, cumulative lifetime cyclophosphamide exposure, treatment adherence, and patient preference.

Recent evidence showed that adding voclosporin or belimumab to standard dual immunosuppression increased treatment efficacy. The immunosuppressive action on T lymphocytes and the stabilizing effect on the podocyte cytoskeleton account for the efficacy of calcineurin inhibitors (CNIs). Triple-immunosuppressive regimens that included

voclosporin or tacrolimus demonstrated increased efficacy in proteinuria reduction compared with standard therapy (3,4). However, caution should be exercised to avoid over-immunosuppression and CNI nephrotoxicity, especially in patients with impaired kidney function due to AKI or CKD. Results from voclosporin trials showed that it had no adverse effect on the eGFR trajectory over time in patients with eGFR over 45 ml/min per 1.73 m² at baseline. Long-term data are required to confirm whether the enhanced efficacy of proteinuria reduction due to CNI translates into improved kidney survival as anticipated. When added to standard therapy, the efficacy of belimumab was evident within 6 months and was sustained for at least 2 years (5). *Post hoc* analysis showed that belimumab treatment was associated with reduced rates of flares and adverse kidney outcomes (6). Although long-term kidney survival data are pending, it is of interest to note that in pivotal trials, the mean eGFR value was numerically higher in belimumab-treated patients compared with controls, whereas the reverse was observed with voclosporin (4,5). The optimal duration and the effect of discontinuing the novel treatments remain to be established.

Progress of the Patient

She was treated with methylprednisolone at 0.5 g/d intravenously for two pulses and then oral prednisone at 0.6 mg/kg per day with gradual tapering and mycophenolate mofetil at 1 g twice daily. Anti-dsDNA and C3 improved, and serum creatinine stabilized at 1.8 mg/dl (eGFR=38 ml/min per 1.73 m²), with proteinuria plateauing at 2.5 g/d after 6 months.

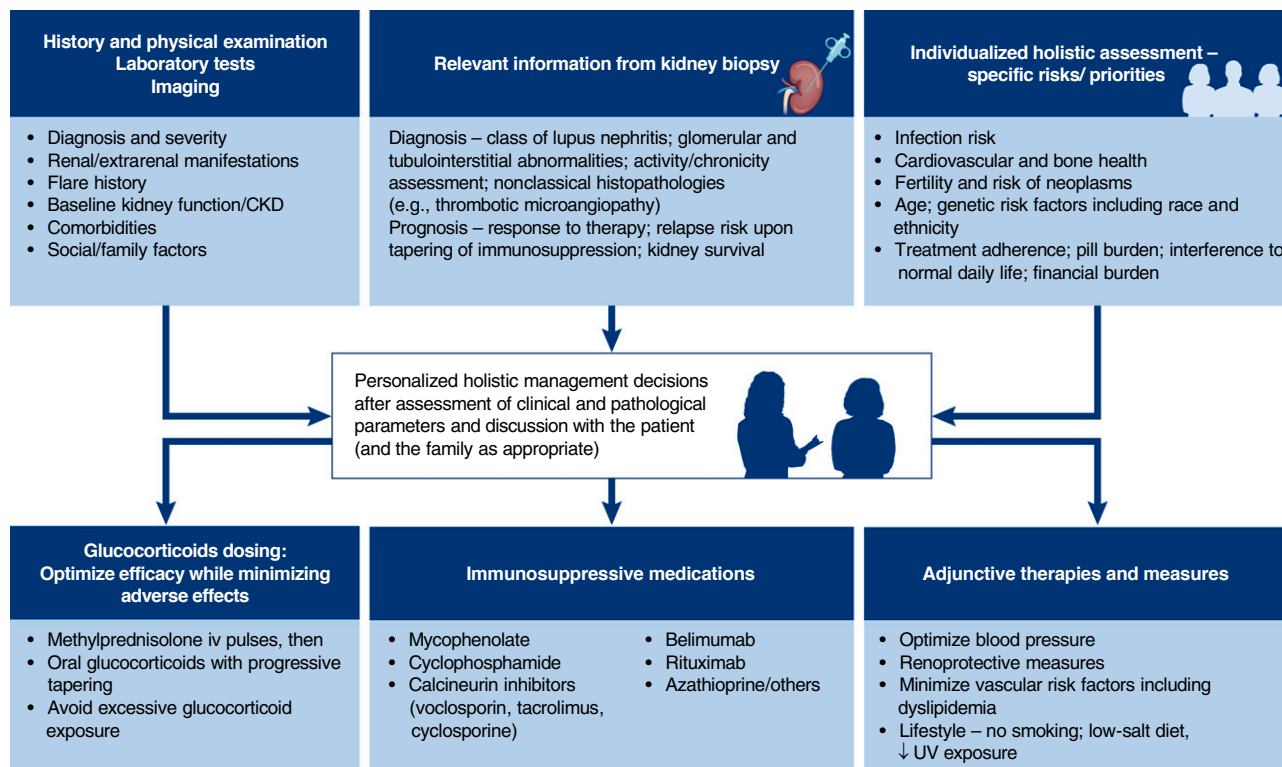


Figure 1. | Personalized management decisions in lupus nephritis. iv, intravenous; UV, ultraviolet.

What to Do If after 4–6 Months of Treatment, Serology and Kidney Function Have Improved, but Proteinuria Is Still Heavy

There is much heterogeneity in the response to therapy. Proteinuria can improve continuously over 12–18 months. Higher overall response rates were reported in Chinese patients, and lower rates were reported in patients of African descent. Unsatisfactory kidney response can be due to unremitting disease activity (due to treatment nonadherence or ineffective therapy) or irreversible kidney scarring, while podocyte injury as in membranous nephropathy can contribute to persistent proteinuria. Ascertaining the factors contributing to unsatisfactory response is a prerequisite to appropriate management. Serologic improvement, which often precedes clinical improvement, is a reassuring sign, but not all patients demonstrate the serologic-clinical correlation. Measuring drug levels can aid in the assurance of adequate exposure and treatment adherence. Repeat kidney biopsy is useful in confirming unabated active disease, for which the management can be a change to an alternative recommended therapy or the addition of a CNI or rituximab. Class 5 lupus nephritis can be associated with slow and/or incomplete resolution of proteinuria after treatment. In contrast to using CNI up front as initial therapy, adding a CNI when proteinuria persisted despite standard therapy has been shown to be efficacious (7).

How to Prevent Further Disease Flares

Prevention of nephritis flares is a key objective in clinical management; flares result in nephron loss and reduced kidney survival, and they subject patients to increased drug toxicities. Risk factors for flares include treatment nonadherence, failure to achieve disease quiescence in the previous flare, and omission of hydroxychloroquine. Although it is generally agreed that maintenance immunosuppression and antimalarial therapy, with gradual and cautious tapering and careful attention to disease activity biomarkers, are important to reduce the disease flare rate, the optimal duration of maintenance immunosuppression remains highly controversial. Absence of active features in repeat kidney biopsy provides reassurance for continued treatment tapering, although the optimal timing of protocol kidney biopsy remains uncertain. The latest Kidney Disease Improving Global Outcomes recommendation favors mycophenolate over azathioprine, in combination with low-dose glucocorticoid, as maintenance immunosuppression (1). The long-term efficacy and safety of mycophenolate maintenance therapy, with a nephritis flare rate of 9% at 5 years and a kidney survival rate of >95% at 10 years, have been reported in Chinese patients (8). Secondary analysis of results from the BLISS-LN trial showed that belimumab reduced the risk of nephritis flare by 55% (6), consistent with previous findings in patients with lupus and without nephritis (9). Although the 2-year flare rate was still significant at 14%, the rate of eGFR decline and the risk of eGFR was reduced by 30% and 40%, respectively, in belimumab-treated patients (6). Considering the promising experience with rituximab in a steroid-sparing regimen (10), the role of novel therapies for “steroid minimization” also warrants further studies (Figure 1).

Management of patients with lupus nephritis entails personalized consideration of clinical and histologic manifestations and a holistic assessment of distinct characteristics pertinent to the efficacy and safety of various treatments and the risk profile for different complications. Nonadherence to treatment remains a leading cause of unfavorable clinical outcomes. Financial barriers also pose a significant challenge to treatment accessibility, especially for new therapies. The importance of rapport and counseling to patients and the family, incorporating both short-term and long-term perspectives, cannot be overemphasized.

Disclosures

T.M. Chan reports consultancy agreements with GlaxoSmithKline and Novartis, research funding from Astellas Pharma Inc. and Baxter, and honoraria from Visterra. J.M. Mejia Vilet reports consultancy agreements with GlaxoSmithKline and Kezar Pharmaceuticals; honoraria from AstraZeneca, Boehringer-Ingelheim, and Roche; and speakers bureau for AstraZeneca, Boehringer-Ingelheim, and Roche. The remaining author has nothing to disclose.

Funding

None.

Author Contributions

T.M. Chan conceptualized the study; T.M. Chan and J.M. Mejia Vilet wrote the original draft; and T.M. Chan, Z.-H. Liu, and J.M. Mejia Vilet reviewed and edited the manuscript.

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Published online ahead of print. Publication date available at www.cjasn.org.