Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis

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The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases was published in 2021. Since then, the pace of drug development for glomerular diseases has accelerated, due in large part to rapidly accumulating insights into disease pathogenesis from genetic and molecular studies of afflicted patients. To keep the Glomerular Diseases Guideline as current as possible, KDIGO made a commitment to the nephrology community to provide periodic updates, based on new developments for each disease. After the 2021 guideline was published, two novel drugs received regulatory approval for the management of lupus nephritis, leading to the first KDIGO guideline update. Herein, an executive summary of the most important guideline changes from the Lupus Nephritis chapter is provided as a quick reference.

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Since publication of the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases,[1] belimumab and voclosporin have been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as add-on immunosuppressives to standard-of-care (SOC) for the treatment of lupus nephritis (LN).[2,3] These additions to the therapeutic armamentarium for the treatment of LN energized patients and providers in the lupus community with the promise of superior response rates compared to SOC alone. At the same time, however, the availability of new therapies raised important questions of how best to apply them. After all, the new therapies are expensive, they do not reduce immunosuppression but increase exposure, and they require patients historically challenged by medication adherence to take even more drugs on a regular basis. Perhaps the most divisive issue has been identifying the profile of an LN patient who needs more than SOC, and whether belimumab or voclosporin would be best for that individual. Because belimumab and voclosporin are poised to significantly change the approach to management of LN, the Lupus Nephritis chapter of the KDIGO 2021 Glomerular Diseases Guideline is the first to be updated (Supplementary Table S1; https://kdigo.org/guidelines/gd/). This Executive Summary provides a brief snapshot of the updated guideline, but all readers are encouraged to view the full chapter for detailed discussion and useful practice points.

The most significant update in the LN guideline was the recommendation for the initial treatment of proliferative LN, which now reads: **We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any *one* of the following: i. mycophenolic acid analogs (MPAA) (*1B*); or ii. low-dose intravenous cyclophosphamide (*1B*); or iii. belimumab and either MPAA or low-dose intravenous cyclophosphamide (*1B*); or iv. MPAA and a calcineurin inhibitor**

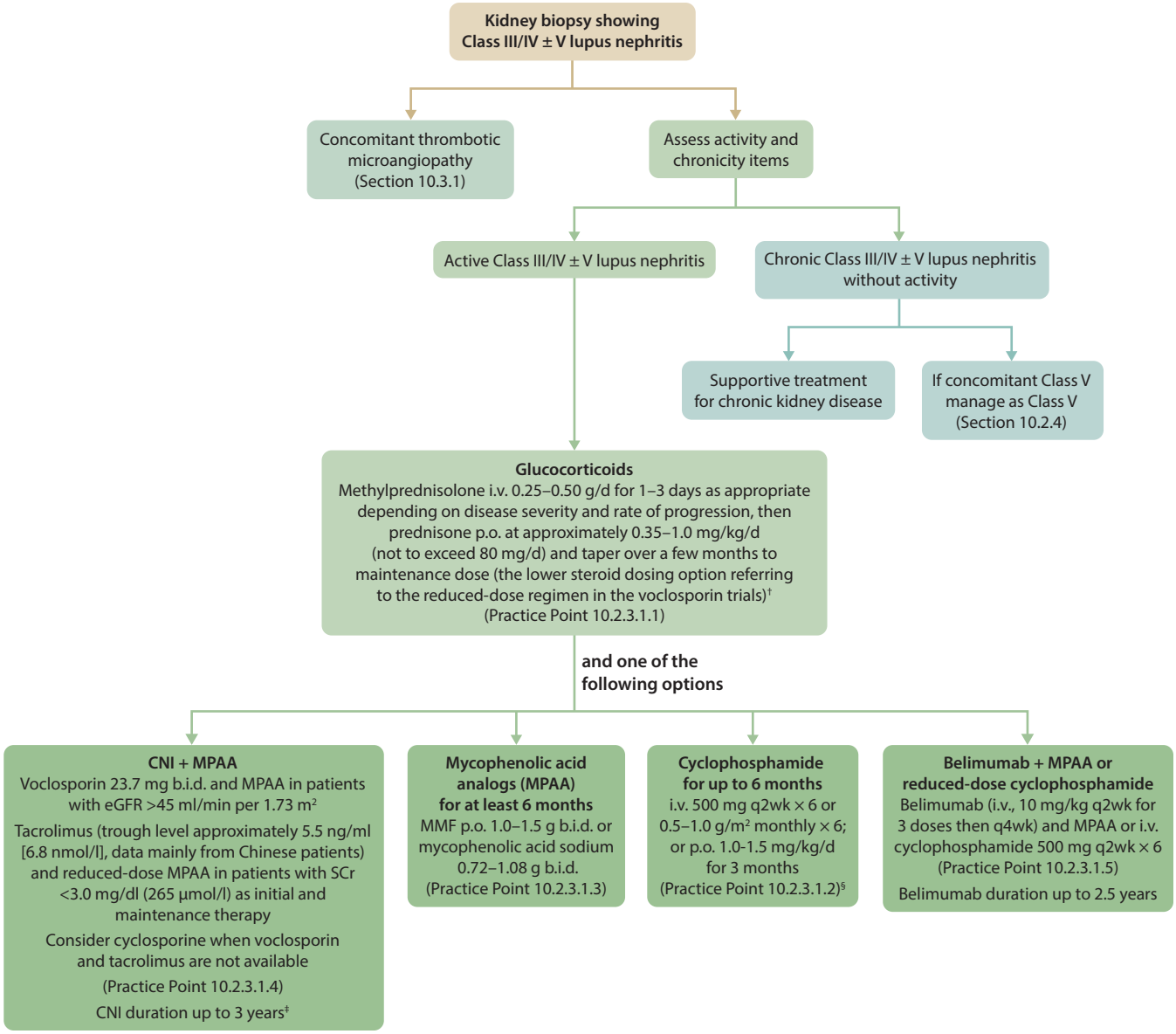

Figure 1 | Recommended approach for initial therapy of active Class III/IV lupus nephritis. Caution is warranted when a calcineurin inhibitor (CNI) is used in patients with significantly impaired kidney function, in view of increased susceptibility for severe consequences due to CNI nephrotoxicity. The estimated glomerular filtration rate (eGFR) and serum creatinine (SCr) levels stated in the figure were patient selection criteria adopted in the respective clinical trials. †Refer to Figure 7 in the full guideline for examples of glucocorticoid treatment regimens. ‡Refer to Figure 9 in the full guideline for durations of CNI or belimumab treatment in clinical trials. §Refer to Figure 6 in the full guideline for comments on cyclophosphamide regimens. b.i.d., twice daily; i.v., intravenous; MMF, mycophenolate mofetil; p.o., oral; q2wk, every 2 weeks; q4wk, every 4 weeks; s.c., subcutaneous.

(CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m²) (*1B*) (Figure 1). Each recommended therapeutic regimen has been graded as 1B, meaning a strong recommendation based on moderate certainty of evidence. The recommendations are based on randomized controlled trials and often more than one randomized controlled trial; however, the results have been downgraded to moderate certainty because of trial limitations such as imprecision in estimated effects for many prioritized outcomes (due to small study size or number of events) and methodological limitations, including lack of blinding in several trials and other risks of bias.

The choice of initial therapy is often based on factors that are not related to specific disease manifestations. These include, but are not limited to, cost, local availability of the therapeutics, local healthcare resources (e.g., availability of infusion suites), likelihood of adherence, prior immunosuppression, fertility concerns, and the presence and severity of chronic kidney disease (CKD). In an idealized healthcare environment where cost and accessibility are not factors, it would be hard to argue against starting treatment with triple

Table 1 | Factors to consider when using United States Food and Drug Administration (FDA)–approved drugs in lupus nephritis

Clinical attributes	Voclosporin	Belimumab
Kidney function	Use cautiously if GFR is impaired (e.g., <45 ml/min per 1.73 m^2)	May be used if GFR is at least 30 ml/min per 1.73 m^2; may slow decline of GFR[a]
Kidney histology	Use cautiously if widespread sclerotic and/or fibrotic changes are present	Not determined
Proteinuria	Effective at any level of proteinuria; may be especially effective in patients with severe proteinuria with significant podocyte damage	More effective in patients with proteinuria <3 g/d
High risk of disease flare	No effect on flare rate	May decrease rate of severe flares
Background immunosuppression	Was not tested in combination with cyclophosphamide	Effective in combination with MMF; uncertain effectiveness in combination with cyclophosphamide
Need for parenteral therapy	Oral only	Intravenous/subcutaneous
Significant extrarenal lupus	Efficacy in extrarenal lupus to be determined	Long track record of efficacy in extrarenal lupus
Safety	Add-on therapy did not increase the incidence of adverse events; monitor acute eGFR variations with voclosporin	Add-on therapy did not increase the incidence of adverse events
Pregnancy	Use not recommended (consider tacrolimus)	Use not recommended

GFR, glomerular filtration rate; MMF, mycophenolate mofetil.
[a]In patients with advanced chronic kidney disease, the benefit of any immunosuppression should be carefully weighed against the likelihood of harm.

therapy given that it has similar safety as dual therapy but better efficacy. Nonetheless, many patients may not need the triple-therapy level of immunosuppression, but identifying such patients *a priori* is not yet possible.

For practitioners who want to use triple therapy, the guideline does offer some suggestions, by way of practice points, to help decide between belimumab and a CNI. For example, a triple-drug regimen with a CNI may be considered in patients with relatively good kidney function (e.g., eGFR ≥45 ml/min per 1.73 m^2) who have heavy proteinuria due to podocyte injury, given the known benefits of CNIs on podocyte structure and function.[4] Alternatively, a triple-drug regimen with belimumab may be considered in patients who are at high risk of LN flare or who have advanced CKD that is likely to progress, based on a *post hoc* analysis of the Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis (BLISS-LN) trial that showed belimumab-treated patients had fewer LN flares and a slower decline in kidney function than patients treated with SOC alone.[5] This same *post hoc* analysis suggested that triple therapy with belimumab worked best on a background of SOC with MPAA, and in patients with non-nephrotic range proteinuria.[5] Examples of clinical situations where one drug may be preferred to the other are given in Table 1.

The randomized controlled trials of triple therapy prompted a reconsideration of maintenance immunosuppression for proliferative LN. Although MPAA remain the maintenance immunosuppressive of choice, the revised LN guideline does indicate patients treated with SOC plus belimumab or a CNI may remain on triple therapy for an extended time. The primary endpoint of the phase 3 belimumab trial was 2 years, but an open-label extension of an additional 28 weeks showed that belimumab-treated patients had a sustained efficacy benefit with no increase in adverse events.[6] Similarly, the endpoint of the phase 3 voclosporin trial was 1 year, but patients doing well on voclosporin received it for 2 additional years with no decline in kidney function and maintenance of proteinuria reduction.[7] Of note, during this 2-year extension, many patients had a reduction in their voclosporin dose, which could have positively impacted eGFR readings.

The immunosuppressive management of pure Class V (membranous) LN remains without definitive recommendations, but rather has only suggested practice points, even though the belimumab and voclosporin trials did include such patients. Voclosporin plus SOC was more effective than SOC alone in patients with Class V LN, but this difference did not quite reach statistical significance, possibly due to a very small number of Class V patients. There were also a small number of Class V patients treated with belimumab plus SOC, and compared to SOC alone, they showed no tendency toward a better rate of remission. Given this, for Class V patients with nephrotic-range proteinuria, the guideline continues to suggest management with glucocorticoid plus MPAA, CNI, or cyclophosphamide, but highlights the need for trials that focus on Class V LN.

Although glucocorticoids are used for the management of LN, there has been considerable effort in the lupus community to reduce cumulative glucocorticoid dosing. The updated guideline pointed out that a limited number of intravenous methylprednisolone pulses given at the start of treatment may allow reduced dosing and more rapid tapering of glucocorticoids in LN, even in the context of conventional therapy.

The updated guideline includes a small but critical new section on CKD progression in LN. Loss of nephron mass occurs with every episode of active LN, putting patients on track toward progressive loss of kidney function, and even kidney failure. Management of patients with LN must include not only immunosuppression for acute treatment of active LN, but also measures to slow or stop CKD progression. While this section is currently limited to blood pressure control, renin-angiotensin-aldosterone system blockade, flare prevention, and nephrotoxin avoidance, it is likely to expand in the future as data on LN and sodium-glucose cotransporter-2 inhibitors or other new agents such as endothelin-A receptor blockers become available.

Finally, there are several additional therapeutics currently being evaluated for the treatment of LN. These novel drugs are in phase 2 and 3 trials. When these trials are completed, hopefully with success, the KDIGO guideline will be updated again to provide the nephrology community with timely evidence-based recommendations for the management of LN.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Table S1. Comparison of the 2021 and 2024 KDIGO Clinical Practice Guideline for the Management of Lupus Nephritis.

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