

## A farewell to the concept of induction and maintenance therapy of lupus nephritis

Presenter: Hans-Joachim Anders, Germany

Chairs: Iva Gunnarsson, Liz Lightstone

Written by: Jasna Trbojevic-Stankovic

Lupus nephritis (LN) is common and one of the most serious manifestations of systemic lupus erythematosus (SLE), with yet undefined optimal management. The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines proposed several treatment options for LN induction and maintenance therapy. Although this concept has been utilized for many years, there are indications that other strategies should be considered.

Due to the autoimmune nature of the disease glucocorticoids and other immunosuppressants are still the cornerstone drugs for its management. Therapy is adjusted individually to mitigate disease activity with the ultimate goal to prevent and control chronicity and organ damage, thus requiring agents beyond immunosuppressants. LN treatment actually involves immunosuppressive therapy targeting the underlying SLE to avoid disease flares and concomitant nephron loss but also measures to attenuate chronic kidney disease (CKD) progression and preserve the remnant nephrons. The latter includes the management of concomitant, non-immunological drivers of CKD progression, such as obesity, diabetes, salty diet, protein diet, pregnancy, etc, that further increase hyperfiltration and metabolic workload of the remaining nephrons. Unfortunately, each SLE and LN flare causes further nephron loss and renal function decline.

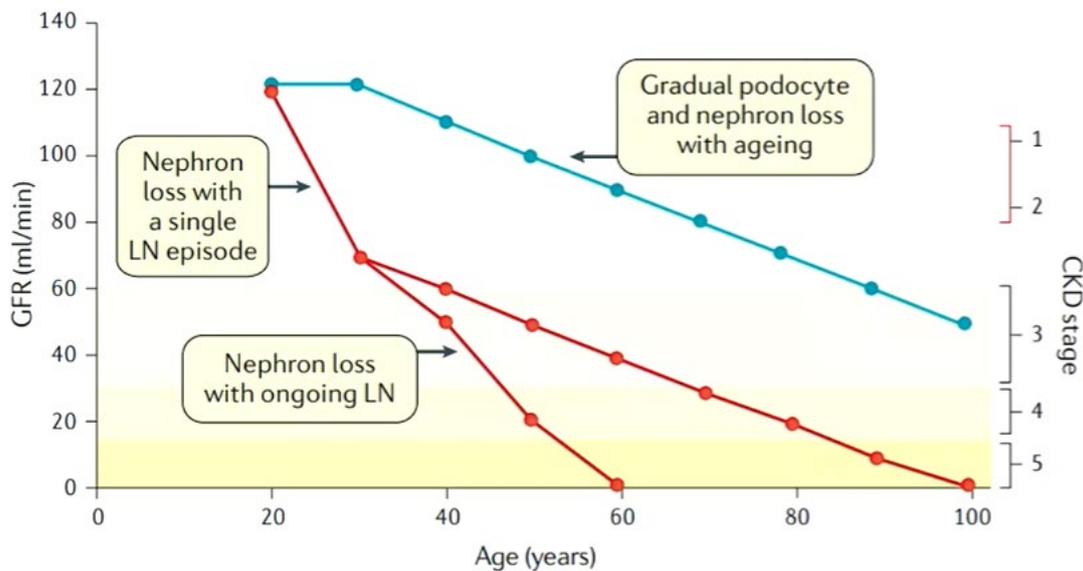


Figure 1. Nephron loss in lupus nephritis

**New concepts of LN treatment**

Rapid and permanent SLE control, persistent CKD treatment, prevention of acute kidney injury, and use of medications with maximum efficacy and minimum toxicity are crucial strategies to improve outcomes in patients with LN. The new concept proposes simultaneous control of autoimmunity and CKD in this population, relying on initial treatment with a combination of methylprednisolone and immunosuppressants, and a subsequent regimen with an adequate dose of the immunosuppressant alone. This concept has already made its way into the official recommendations, such as the 2019 Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) guidelines. Thus, the new concept abandons the terms “induction” and “maintenance” therapy and embraces the definitions “initial” and “subsequent” treatment. The evidence supporting this new concept of LN management can be found in several trials.

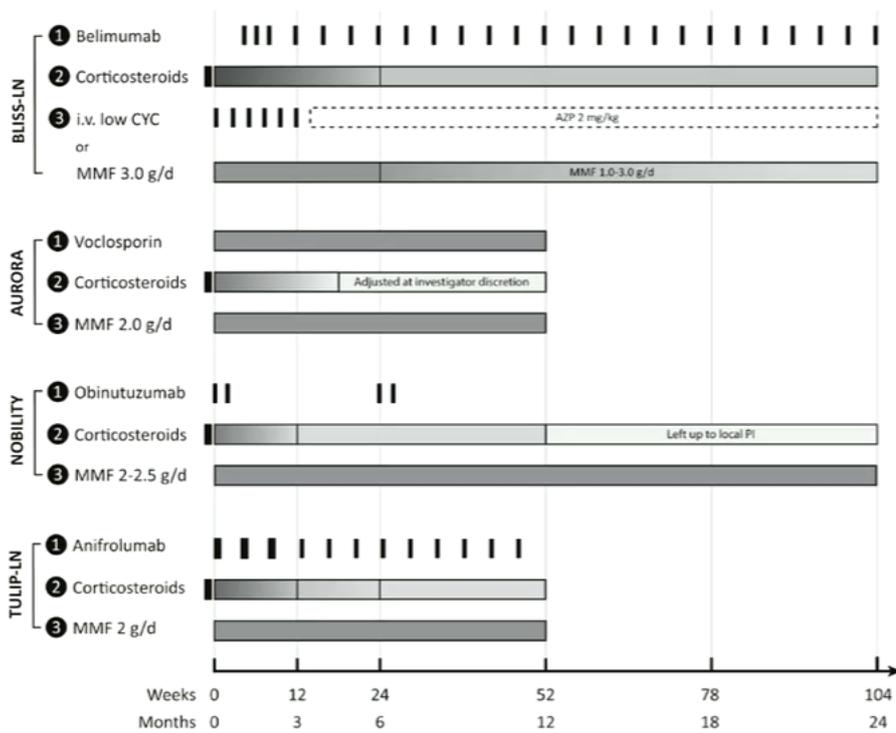


Figure 2. Novel combination therapies for lupus nephritis in recent trials

The BLISS-LN trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial, conducted in 21 countries to assess the effects of belimumab in LN patients. Belimumab was continuously added to the combination of cyclophosphamide or mycophenolate-mofetil (MMF) and corticosteroids in the intervention group, while controls received a placebo on the background of the same standard therapy. Results showed that belimumab mainly affected the spleen and lymph nodes and the impact on the renal endpoints was moderate. Still, the renal results were encouraging given the achieved proteinuria reduction over the course of two years. Belimumab reduced LN flares and had a slight positive impact on the decline of the estimated glomerular filtration rate (eGFR). In terms of safety, belimumab has been used for over ten years and there have been no infections or vaccine reactions. The suicidality issue related to this agent that arose in one of the earlier trials did not recur. Given all the above, belimumab is eligible in patients with proliferative LN, pronounced humoral disease activity and lower proteinuria (<3g/24h).

Voclosporin is a novel calcineurin inhibitor that has recently been approved as an adjunct treatment for LN. Its particular design allows for a more predictable pharmacokinetic profile than other calcineurin inhibitors and does not require monitoring of blood levels. This agent has been evaluated in the AURORA 1 multicentre, double-blind, randomised phase 3 trial across 27 countries. Patients were randomly assigned to oral voclosporin or placebo, on a background of MMF and rapidly tapered low-dose oral steroids. Over the 2-year follow-up, voclosporin exhibited a direct and quick antiproteinuric effect by reducing T cell activation and stabilizing podocyte resilience. It also stabilized renal function, but it remained unclear whether it can prevent LN flares. The safety profile was favourable and there was no evidence of nephrotoxicity or adverse metabolic events during the follow-up. Since the trial focused on active LN, there is scarce data on non-renal SLE to permit comparison with belimumab.

Encouraging results have recently been published from the NOBILITY trial, currently in phase 2, which evaluated obinutuzumab, a cytolytic antibody directed at CD20, as a potential treatment for LN. Similar to belimumab, obinutuzumab affects both B and T cells and has an antiproteinuric effect evident after six months of use. The promising news is that after two years of follow-up of continuous, once every six months, administration of obinutuzumab on top of standard care with MMF and corticosteroids in LN patients there was also an improvement in the eGFR. The strong impact on SLE biomarkers strongly suggests that this approach could become a new treatment option once the phase 3 trial is completed.

The TULIP-LN trial tested anifrolumab, a monoclonal antibody that targets the anti-interferon- $\alpha$  receptor, as a continuous treatment. This agent suppresses the expression of interferon alpha-1-dependent genes in SLE and antiviral host defence. Animal model trials have shown a good response to anifrolumab in non-renal SLE, leading to its approval based on TULIP-1 and TULIP-2 trials. However, in the TULIP-LN trial anifrolumab did not show a significant effect on proteinuria, even though some of the secondary endpoints, including a complete renal response with inactive urinary sediment and urine protein-creatinine ratio  $\leq 0.5$ mg/mg, were achieved. Blocking the interferon system decreased antiviral host defence, which was clinically relevant. The incidence of herpes zoster with anifrolumab was double that in the placebo group and over ten times that in non-renal SLE, indicating that LN patients are considerably more immunodeficient than those with non-renal SLE.

Dapagliflozin is an SGLT2 inhibitor already approved for patients with diabetes mellitus and/or heart failure, as well as those at risk for CKD progression and cardiovascular diseases. It acts by blocking the sodium-glucose channel in the proximal tubule, thus preventing the reabsorption of glucose and sodium, reducing metabolic workload and improving hemodynamics, while reducing hyperfiltration and alleviating the strain on the remaining nephrons. It is believed that LN patients may also benefit from this drug, but further research is needed relating to potential side effects such as urogenital infections, which may be more likely in LN patients taking immunosuppressants.

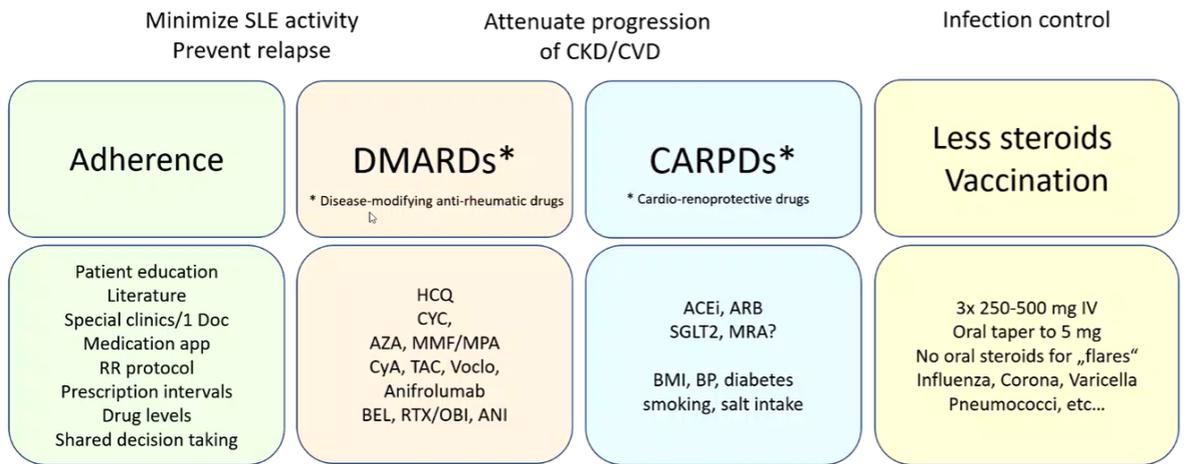


Figure 3. Proposed treatment concept for lupus nephritis

To summarize, the new treatment approach for LN should aim to minimize SLE activity, prevent relapses, slow the progression of CKD and cardiovascular diseases, and control infections. In addition to disease-modifying anti-rheumatic drugs, LN patients should receive cardio-reno-protective drugs such as RAS inhibitors and SGLT2 inhibitors. Mineralocorticoid receptor antagonists (MRAs) can also be used to reduce inflammation and fibrosis in the kidney remodelling process that occurs in LN. Furthermore, attention should be focused on smoking cessation, diabetes and blood pressure control, adherence to therapy, and vaccination in these patients.

**Key points**

1. Treatment of LN requires consideration of both immunosuppressive therapies for underlying SLE and interventions to slow CKD progression.
2. Ongoing trials are evaluating the efficacy and safety of combination therapies with belimumab, voclosporin, obinutuzumab and anifrolumab in LN patients.
3. The ultimate goal of LN treatment is to achieve rapid and permanent control of underlying SLE, protect the remaining nephrons, boost the efficacy and curtail the toxicity of applied medications.

### Further reading

- (1) Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int.* 2021;99(3S):S1-S87. doi: 10.1016/j.kint.2020.11.003.
- (2) Lech M, Anders HJ. The pathogenesis of lupus nephritis. *J Am Soc Nephrol.* 2013;24(9):1357-1366. doi:10.1681/ASN.2013010026
- (3) Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis.* 2020;79(6):713-723. doi:10.1136/annrheumdis-2020-216924
- (4) Anders HJ, Lei Y, Rovin BH. Induction and maintenance therapy of lupus nephritis: an obituary. *Kidney Int.* 2021;99(2):288-291. doi: 10.1016/j.kint.2020.11.009.
- (5) Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. *Nat Rev Dis Primers.* 2020;6(1):7. doi: 10.1038/s41572-019-0141-9.
- (6) Lech M, Anders HJ. The pathogenesis of lupus nephritis. *J Am Soc Nephrol.* 2013;24(9):1357-66. doi: 10.1681/ASN.2013010026.