Correspondence on 'EULAR recommendations for the management of systemic lupus erythematosus: 2023 update' by Fanouriakis *et al*

The recently published European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of systemic lupus erythematosus (SLE) (2023 update)[1] recognise the major achievements in treating lupus nephritis (LN). These include the approval of two newer agents, belimumab and voclosporin, which can be used as add-on therapies and have proved effective in the phase III trials BLISS-LN and AURORA-1.[2 3] In BLISS-LN, which randomised 448 patients, a urine protein-to-creatinine ratio (UPCR) of ≤0.7 g/g creatinine was part of the primary efficacy renal response and was reached by 99 (44.4%) and 75 (33.6%) in the belimumab and placebo arms, respectively, at 104 weeks.[2] A component of the primary endpoint of AURORA-1, which randomised 357 patients, was the achievement of a UPCR≤0.5 g/g creatinine and this was reached by 81 (45.3%) and 41 (23.0%) in the voclosporin and placebo arms, respectively, at 52 weeks.[3] These proteinuria endpoints are based on recommendations issued by EULAR and the European Renal Association (ERA), which included proteinuria <0.5–0.7 g/day at 12 months in the definition of complete renal response.[4] This recommendation is based on evidence from observational studies identifying a proteinuria cut-off of 0.7–0.8 g/day at 12 months to be predictive of medium-to-long-term 'preservation' of kidney function in patients with LN.[5]

Kidney Disease: Improving Global Outcome, however, has defined individuals with an albuminuria >0.3 g/day (proteinuria >0.5 g/day) and an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 at high risk to develop kidney failure and those with an eGFR below 59 mL/min/1.73 m^2 at very high risk. The presence of residual albuminuria labels a patient as having chronic kidney disease (CKD) and this nomenclature of CKD has also been incorporated into the KDIGO 2024 Clinical Practice Guideline for the management of LN.[6] Indeed, individuals with LN and established CKD had an annualised eGFR decline of 4.4 mL/min/1.73 m^2 in comparison to a decline of 0.7 mL/min/1.73 m^2 of patients with SLE with a comparable eGFR but without LN.[7] The relevance of such a progressive decline in eGFR has been studied in the Hopkins Lupus Cohort comprising 2528 patients with SLE. The risk of kidney failure within 20 years was 8.4% in the overall cohort, but 20% in those who experienced proteinuria within the first year of a SLE diagnosis.[8] This highlights that the risk to develop kidney failure is similar in LN when compared with a 'normal' CKD population. Registry data from Canada indicated that individuals with an eGFR ≥60 mL/min/1.73 m^2 and an albuminuria >0.3 g/day have a rate of kidney failure of 1.0 per 1000 person-years, in comparison to 0.03 without albuminuria.[9] It is likely that the underlying processes leading to a progressive decline in kidney function in LN mimic adaptive strategies as observed in a general CKD population, including glomerular hyperfiltration and a secondary loss of nephrons.

CKD has been a field of major advances over the past decade, but clinical trials have traditionally involved patients at advanced age (>60 years) with diabetic kidney disease and other comorbidities such as hypertension. The widespread use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) is based on two pivotal trials, DAPA-CKD and EMPA-KIDNEY. Patients with heavy immunosuppression and/or individuals with LN (DAPA-CKD) have been excluded from participation based on the fear of an increased risk of urinary tract infections and other rare infectious complications reported in SGLT2i-users such as Fournier gangrene.[10] The steps leading to CKD in most patients involved in DAPA-CKD and EMPA-KIDNEY differ from the aetiopathogenesis of CKD in LN, where patients present with abnormalities (either reduced eGFR, persistent proteinuria or both) at an earlier stage of life. Plus, both trials in CKD have included patients with a body mass index ≥29 kg/m^2, indicating that the remnant nephron mass of these patients was at risk to develop glomerulosclerosis.[11 12] The management of CKD not only involves pharmacological interventions[13] but also includes dietary and lifestyle adjustments, such as reduction in salt and protein intake, cessation of smoking and exercise to reduce body weight and to achieve blood pressure control. The EULAR recommendations for the management of SLE provide an overview of treatment options and mention that SGLT2i might be considered in patients with decreased eGFR. Patients with established LN should receive optimised nephroprotective measures for CKD beyond solely pharmacological interventions. Here, we would also stress that especially those with persistent proteinuria might benefit from prescription of SGLT2i on top of renin–angiotensin–aldosterone system inhibitors, once other interventions have not been successful to reduce proteinuria. Notably, individuals with an albuminuria of 0.3–1.0 g/day in EMPA-KIDNEY achieved an annual eGFR decline of 1.42 mL/min/1.73 m^2 in the empagliflozin arm as compared with 2.78 mL/min/1.73 m^2 in the placebo arm when the chronic slope, defined as eGFR measurement 2 months after therapy initiation to the final visit, was assessed.[14] These effects were consistent in all albuminuria groups, indicating that SGLT2is are potent agents to reduce glomerular hyperfiltration and thus preserve kidney function in the long term. Further agents will eventually enter the market, but we argue that emphasis on CKD management is one of the unmet needs in LN recommendations/guidelines and should be incorporated in future updates. Besides beneficial effects on kidney outcomes, the combination of different agents to prevent CKD progression also confers benefits in the prevention of major adverse cardiac events (MACE),[15] a well-known problem in patients with SLE. This is particularly relevant as even newer agents approved for LN management fail to reduce proteinuria <0.5 g/day in a majority of patients. To conclude, data on SGLT2i use in LN are still limited; besides retrospective data reporting efficacy, defined as ≥30% proteinuria reduction in 20 out of 32 patients (62.5%),[16] a phase I/II trial of 17 Chinese patients mainly providing data on safety,[17] and animal data even highlighting anti-inflammatory processes,[18] which need to be confirmed in independent investigations. Further data are required to prove safety and efficacy of these agents in patients with LN, but until then a 'shared decision-making' with the patient about potential initiation of SGLT2i is required.

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