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What's new in Lupus Nephritis: from guidelines to real-world practices

A promotional symposium organised and funded by Otsuka Pharmaceutical Europe Ltd at the 61st European Renal Association (ERA) Congress

ES-LUP-2400159 v1
Fecha de elaboración: julio 2024

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The Otsuka-sponsored satellite symposium *"What's new in Lupus Nephritis: from guidelines to real-world practices"* was held on 25 May 2024 at the 61st European Renal Association (ERA Congress in Stockholm, Sweden and virtually.

A renowned faculty of experts from across Europe considered the implications of recent guideline updates for the management of Lupus Nephritis (LN), examine clinical and real-world evidence for the use of contemporary LN therapies and discuss current 'hot' topics of interest in the field of LN.

Faculty

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Nephrology Clinician-Scientist at the Department of Internal Medicine of the Leiden University Medical Center (LUMC), the Netherlands

Professor Margherita Zen

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Professor Annette Bruchfeld

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Key recent trials and guidelines in lupus nephritis

Professor Annette Bruchfeld

Professor Bruchfeld began by highlighting some of the overarching principles from the 2023 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of systemic lupus erythematosus (SLE).[1] Of note, SLE disease activity should be assessed at each visit, and organ damage should be evaluated at least annually. Choice of treatment should be informed by patient characteristics, type and severity of organ involvement, risk of progressive organ damage and treatment-related harms, alongside other factors. Early diagnosis of SLE and prompt initiation of treatment aiming for remission (or low disease activity if this is not possible) are essential to prevent flares and organ damage, improve prognosis and enhance quality of life (QoL).[1]

Patient outcomes with current standard of care (SoC) therapies for LN are often not optimal. Only 20–30% of patients achieve a complete renal response (CRR) within 1 year,[2,3] and in Professor Bruchfeld's experience 20-35% of patients who do not respond will relapse within 3–5 years.[4] LN flares can induce cumulative kidney damage leading to chronic kidney disease (CKD),[5] and 5–20% of patients develop end-stage kidney disease (ESKD) within 10 years of initial LN diagnosis.[4] Therefore, improving the prognosis of patients with LN is crucial.

In terms of LN management, some of the key changes in the 2023 updated EULAR recommendations are: (1) use a lower glucocorticoid maintenance target of ≤5 mg/day and fully withdraw glucocorticoids whenever possible; (2) consider the use of early combination treatment with either belimumab or a calcineurin inhibitor (CNI) as part of initial therapy; and (3) continue treatment for at least 3 years after achieving a renal response.[6]

The 2024 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the management of LN includes several updates relating to glucocorticoid dose and use of biologics.[7] Early combination therapy with either belimumab or a CNI (particularly voclosporin or tacrolimus) should be considered as part of initial therapy. This triple regimen can be continued as maintenance therapy for 2–3 years.[7] A triple immunosuppressant regimen may be preferred for patients with repeated renal flares or at high risk of progression to kidney failure due to severe CKD. Finally, a glucocorticoid maintenance target of <5 mg/day should be used, and glucocorticoid discontinuation considered when CRR is sustained for ≥1 year.[7]

Voclosporin is a CNI that inhibits T-cell activation and stabilises podocytes in the kidney.[8,9] In the Phase 3 AURORA-1 trial in patients with LN (N=357 patients with

active LN), voclosporin in combination with mycophenolate mofetil (MMF) and low-dose glucocorticoids led to a clinically and statistically superior CRR rate compared with MMF and low-dose glucocorticoids alone (41% vs 23%; p<0·0001) (**Table 1**).[10] Subgroup analyses of the primary endpoint at Week 52 resulted in odds ratios (ORs) greater than 1 indicating a higher CRR rate with voclosporin versus the placebo group in all subgroups studied. Results in the white and pure class V subgroups were non-significant. In the AURORA-2 long-term extension trial, the corrected estimated glomerular filtration rate (eGFR) slope from Month 12 (used to evaluate long-term kidney function) was –0.2 mL/min/1.73 m^2 (95% confidence interval [CI] –3.0 to 2.7) in the voclosporin group and –5.4 mL/min/1.73 m2 (95% CI –8.4 to –2.3) in the control group.[11]

Belimumab is an antibody directed against soluble B-cell activating factor (BAFF)/B-lymphocyte stimulator (BlyS) that affects B-cell development, maturation, survival and antibody production.[12] In the Phase 3 BLISS-LN trial (N=448 patients with active LN), at Week 104, significantly more patients in the belimumab group than in the placebo group had a primary efficacy renal response (PERR) at Week 104 (43% vs 32%; p=0.03).[13] In a secondary analysis of BLISS-LN that examined the effects of belimumab on kidney outcomes and preservation of kidney function, belimumab was found to be most effective in improving the PERR in patients with proliferative LN and a baseline urine protein creatinine ratio (UPCR) <3 g/day. There was no improvement in kidney response with belimumab treatment in patients with LN and sub-epithelial deposits or with a baseline UPCR of ≥3 g/day. However, belimumab reduced the risk of kidney-related events or death regardless of proteinuria levels.14 Belimumab was well tolerated for the treatment of LN.[13]

Professor Bruchfeld ended by discussing combination therapy, noting that the choice of therapy should take into consideration the preferences of the patient and physician, efficacy, safety, patient comorbidities and other individual characteristics.

Voclo smpc Voclosporin	Voclosporin group (n=179)	Placebo group (n=178)	OR OR HR (95% CI)	p-value
Primary endpoint				
	73 (41%)	40 (23%)	OR 2.65 (1.64-4.27)	<0.0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2.23 (1.34-3.72)	0.002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	50%) OR 2.43 (1.56-3.79)	<0.001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2.26 (1.45-3.51)	<0.001 <0.001
Time to UPCR 50.5 mg/mg, days	169 (11-214)	372 (295-NC)	HR 2.02 (1.51-2.70)	<0.001
Time to 50% reduction in UPCR, days	29 (29-32)	63 (57-87)	HR 2.05 (162-260)	<0.001

Table 1. AURORA 1 – key efficacy results[10]

Please refer to Lupkynis Summary of Product Characteristics (SmPC): https://cima.aemps.es/cima/publico/detalle.html?nregistro=1221678001#3
Table adapted from Rovin et al. (2021).
Data are n (%) or median (95% CI), unless otherwise specified.
CI, confidence interval; HR, hazard ratio; MMF, mycophenolate mofetil;
OR, odds ratio; NC, non-calculable;
UPCR, urine protein creatinine ratio.

Two years of experience in lupus nephritis with the latest therapies in a real-world setting

Professor Margherita Zen

Real-world evidence complements data from clinical trials and provides valuable insights into the use of treatments in daily practice. Professor Zen discussed experience with real-world use of contemporary LN therapies (rituximab, belimumab, tacrolimus and voclosporin) from Italian multicentre cohort studies and the University of Padua Lupus Cohort.

An analysis of data from the Italian Multicentre Registry was conducted that included 134 patients with SLE treated with off-label rituximab at 11 centres.[15] After the first course of rituximab, CRRs and partial renal responses were observed in 30.9% and 63.2% of patients, respectively, after 12-months of follow up. Mean 24-hour proteinuria decreased over time and was significantly lower at 3, 6 and 12-months of follow up versus baseline. Adverse events (AEs) were reported in 23.9% of patients after the first rituximab course and 33.3% of patients after retreatment.[15] In a study of 91 patients with LN in the belimumab Italian Registry, BeRLiSS-LN, at 24 months, 66.1% of patients achieved a PERR and 37.3% achieved a CRR.[16] Multivariable analysis showed that hypertension, high baseline serum creatinine and high baseline proteinuria were negatively predictors of PERR. In total, 217 AEs were reported in 63 patients.[16]

Since 2017, 19 patients with LN have been treated with tacrolimus at Padua University. The majority of patients were refractory to SoC therapies. In 80% of patients, tacrolimus was used in combination with MMF and in 20% of patients as monotherapy during pregnancy. Following treatment, mean 24-hour proteinuria decreased from 4.5 g/day at baseline to 2 g/day at 6 months and 1.5 g/day at 12 months, and 20% of patients achieved a CRR at 12 months.[17] Since its approval in 2023, six patients have been treated with voclosporin at Padua University. Of these, four have class IV LN, five have failed on MMF as induction therapy, three have failed on MMF plus belimumab in combination, two have failed on rituximab and two have failed on tacrolimus. Mean 24-hour proteinuria at baseline was 2.45 g/day, decreasing to 0.9 g/day at 2 months and 0.8 g/day at 3 months after treatment initiation. Four patients (80%) achieved ≥50% reduction in proteinuria at 3 months and eGFR remained stable in all patients. There was no worsening in comorbidities (hypertension or dyslipidaemia).[17]

Professor Zen concluded that data from Italian multicentre registries and the University of Padua Lupus Cohort confirm the efficacy of contemporary therapies for LN, although a significant proportion of patients still fail to achieve remission.

Hot topics in lupus nephritis

Kidney protection

Professor Annette Bruchfeld

LN is associated with an increased risk of morbidity, primarily related to cardiovascular disease and infections, and mortality related to CKD and ESKD.[4] Challenges remain regarding the efficacy and toxicity profiles of current SoC therapies. The goals of LN therapy are to avoid progression of CKD to ESKD, achieve complete renal remission, treat residual inflammation, avoid flares, limit drug toxicity and improve QoL.[18] Each LN flare causes irreversible nephron loss[4] and there is continued loss with ongoing LN (**Figure 1**). Therefore, it is important to consider the lifetime risk of CKD, particularly as many patients with LN are diagnosed at a young age.

An analysis of data from the Hopkins Lupus Cohort (N=2,528) found that the overall incidence of kidney failure within 20 years of SLE diagnosis was 8.4%.[19] The risk was increased by 20.0% among patients who experienced proteinuria within the first year of diagnosis.

Demographic predictors of kidney failure included African-American ethnicity and age ≥40 years at SLE diagnosis. Among immunologic markers, low C3 complement level was a strong predictor of kidney failure. In a study of 504 patients diagnosed with SLE within the first year and followed for an average of 11 years, the risk of progressive CKD was relatively low in the absence of nephritis. Progressive loss of kidney function, and CKD developed exclusively in patients with LN who had persistent proteinuria and dyslipidaemia.[20]
Research has also shown that the risk of mortality, cardiovascular events and progression to ESKD associated with any given level of eGFR is independently increased in patients with higher levels of proteinuria.[21]

Professor Bruchfeld considered whether proteinuria could be considered a reliable outcome measure, and the value of repeat kidney biopsy. In a study of 25 patients with LN who had undergone two or more kidney biopsies, 60% of patients with no activity on biopsy had ongoing proteinuria (>500 mg/day), and 30% had significant activity at the last biopsy, despite reduction of proteinuria to <500 mg/day.[22] A prospective observational study was conducted in patients with LN in complete clinical remission for at least 12 months, who had consented to a second kidney biopsy, were tapered off maintenance immunosuppression and were followed for LN flares over 24 months.[23] Of 36 patients who completed the study, LN flares occurred in 11 patients, and 10 of these had residual histologic activity on the second biopsy. The investigators concluded that persistent histologic activity on kidney biopsy after

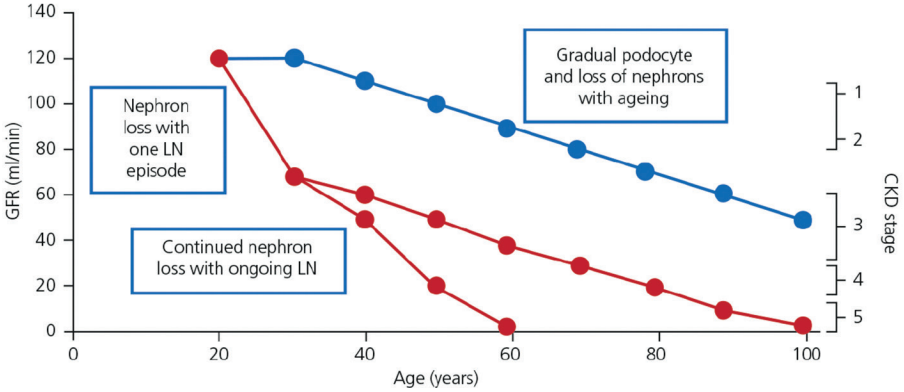

Figure 1. Lifetime risk of ESKD in patients with LN[4]

Figure adapted from Anders *et al.* (2020).
CKD, chronic kidney disease; GFR, glomerular filtration rate; LN, lupus nephritis.

clinical remission is associated with future LN flare, particularly if the activity index is greater than 2.[23] Withdrawal of immunosuppression appears to be reasonable for patients with no histologic activity on kidney biopsy. Thus, repeat biopsy may be a useful guide for treatment decision making in patients with LN.

Treatments that delay progression of CKD with a strong evidence base include renin-angiotensin system inhibitors (RASi) and sodium-glucose transport protein 2 inhibitors (SGLT2i), which may reduce intraglomerular pressure through their respective effects on efferent and afferent arteriolar tone.[24] Combining these two drugs may further reduce intraglomerular pressure. In a retrospective, observational, international cohort study in 493 patients with biopsy-proven glomerular diseases (including LN) on background therapy with RASi, the use of SGLT2i was associated with a significant reduction in proteinuria.[25]

Hot topics in lupus nephritis
Need for reduction of steroids

Professor Margherita Zen

Increased morbidity and mortality, and poor clinical outcomes, in patients with SLE may be due to continuous organ damage accrual resulting from persistent disease activity and prolonged glucocorticoid exposure (**Figure 2**).[26] Even low daily doses of glucocorticoids are associated with AEs, and these are both dose- and time-dependent.[27–29] Balancing the need to control disease activity and avoid flares with the need to reduce glucocorticoid use presents a challenge for clinicians.

In a Canadian study, inception patients from the University of Toronto Lupus Clinic who had never taken glucocorticoids and had a minimum of 3 years of follow up, were compared with patients who received glucocorticoids within the first 6 months of SLE diagnosis and had continued treatment for at least 3 years.[30] Patients exposed to glucocorticoids accrued more organ damage compared with glucocorticoid-naïve patients, independent of disease activity.[30] Another study of 293 patients with SLE during 7-years of follow up found that among those patients who achieved ≥5-year remission, patients in clinical remission off glucocorticoids or in complete remission accrued less damage ($p<0.001$) than patients in clinical remission on glucocorticoids.[31]

Professor Zen concluded that by discussing nascent therapies for LN that have shown the ability to control disease activity, and may also allow a reduction in glucocorticoid burden. The AURORA-1 trial of voclosporin used a rapid, low-dose oral glucocorticoid taper that included intravenous methylprednisolone on Days 1 and 2; oral glucocorticoid was initiated on Day 3 with 20–25 mg/day prednisone and tapered to a target dose of 2.5 mg/day at Week 16.10 Even with this rapid reduction in glucocorticoids, voclosporin in combination with MMF and low-dose glucocorticoids led to a significantly higher CRR rate compared with MMF and low-dose glucocorticoids alone, with a comparable safety profile.[10]

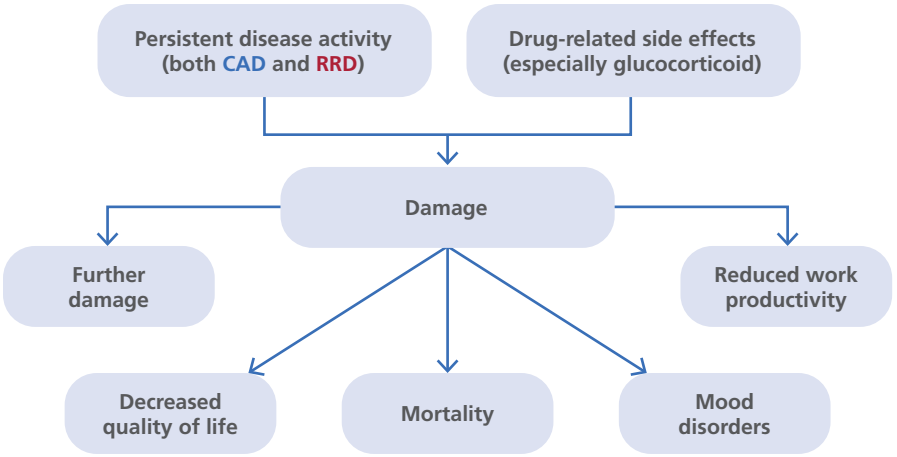

Figure 2. Determinants of damage and poor outcomes in SLE[26]

CAD, chronic active disease; RRD, relapsing-remitting disease.

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