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European Renal Assoc

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The management of lupus nephritis as proposed by EULAR/ERA 2019 versus KDIGO 2021

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ABSTRACT

In 2019 and 2021, the European League for Rheumatism (EULAR) jointly with the European Renal Association (ERA) and the Kidney Disease: Improving Global Outcomes (KDIGO), respectively, released updated guidelines on the management of lupus nephritis (LN). The Immunology Working Group of the ERA reviewed and compared both updates. Recommendations were either consistent or differences were of negligible clinical relevance for: indication for kidney biopsy, kidney biopsy interpretation, treatment targets, hydroxychloroquine dosing, first-line initial immunosuppressive therapy for active class III, IV (\pm V) LN, pregnancy in LN, LN in paediatric patients and LN patients with kidney failure. Relevant differences in the recommended management relate to the recognition of lupus podocytopathies, uncertainties in steroid dosing, drug preferences in specific populations and

maintenance therapy, treatment of pure class V LN, therapy of recurrent LN, evolving alternative drug options and diagnostic work-up of thrombotic microangiopathy. Altogether, both documents provide an excellent guidance to the growing complexity of LN management. This article endeavours to prevent confusion by identifying differences and clarifying discrepancies.

Keywords: autoimmunity, glomerulonephritis, inflammation, lupus, standards

INTRODUCTION

Lupus nephritis (LN) is a frequent complication of systemic lupus erythematosus (SLE), a systemic autoimmune disease affecting mostly young women [1]. LN has significant impact on the morbidity and mortality of SLE, in particular when a late diagnosis or insufficient control of disease activity leads to chronic kidney disease (CKD) or ultimately kidney failure [1]. In addition, LN and LN-related CKD affect fertility and pregnancy outcomes and cardiovascular morbidity and mortality later in life. Therefore, early diagnosis, rapid and effective treatment, and sustaining an immunological response

are essential to improve both short- and long-term outcomes of patients with LN.

Multiple stakeholders have sought to improve management and to expand treatment options for patients with LN. Indeed, the last decade has seen numerous clinical trials, biomarker studies and longitudinal outcome analyses in these areas. Furthermore, several organizations and societies have released recommendations for the management of LN, and periodically update them based on evolving scientific evidence.

The European League Against Rheumatism (EULAR) and the European Renal Association (ERA, formerly ERA-EDTA) joined forces and originally released recommendations for the management of adult and paediatric LN in 2012 [2]; these were updated in 2019 (published in 2020) [3]. To reach a consensus, 11 rheumatologists, 11 nephrologists (including one paediatric), 1 allied health professional and 2 patient representatives followed a Delphi-based methodology with dedicated staff who performed a systematic review of the literature on 15 pre-selected questions regarding the topic. The panel discussed the available evidence before assessing the level of agreement for each topic. The guideline consists of a list of overarching principles and specific recommendations equipped with the respective levels of evidence, grading of recommendations and levels of agreement.

The Kidney Disease: Improving Global Outcomes initiative (KDIGO) released a guideline for the management of the various forms of glomerulonephritides, including LN, in 2012 [4], with an update produced in 2021 [5]. KDIGO gathered a global panel of multidisciplinary clinical and scientific experts who first convened in 2017 at a Controversy Conference to identify key questions, which were published to gain broad feedback of the community. A designated Evidence Review Team systematically reviewed and analysed the evidence and used the GRADE approach to analyse certainty of the evidence and the strength of the guideline recommendations. A draft was made available for public review, and the feedback was implemented into the final version. The guideline lists 'recommendations' based on clear evidence as well as 'practice points' to provide guidance where sufficient evidence is missing.

Of note, KDIGO 2021 considered scientific evidence that was not yet available at the time of EULAR/ERA 2019 and the EULAR-ERA expert panel included 50% rheumatologists, whereas at KDIGO, rheumatology was less well represented. In addition, the three organizations target different audiences: EULAR and ERA address mostly aspects related to European patient populations and healthcare systems, whereas KDIGO has a global mission and outreach and therefore received input from experts from all world regions.

The board of the Immunonephrology Working Group of the ERA reviewed the two guidelines to establish if and how some of the differences may impact upon clinical practice.

RECOMMENDATION TOPICS

Indication for kidney biopsy

Proteinuria is one of several indications for kidney biopsy and the two guidelines slightly differ in terms of how to assess proteinuria. EULAR/ERA recommend proteinuria assessment

by urinary protein/creatinine ratio (UPCR) with a cut-off of >500 mg/g on spot urine analysis (>0.5 g/day assessed by 24-h urine sampling). On the other hand, KDIGO advocates UPCR measurement in an attempted 24-h urine collection as the preferred method for quantifying proteinuria, and subsequently interpreting the results based on the complete clinical context (Table 1).

UPCR cannot be directly converted into 24-h albumin excretion, as UPCR also depends on muscle mass and 24-h albumin excretion is not adjusted for body size. We favour UPCR as it is easier to perform, but performing UPCR in a urine collection over several hours can avoid errors. Spot urine analysis is a useful tool for nephritis screening and can prompt more detailed urine analysis. Additionally, fever, diabetes, obesity, pregnancy, hypertension and a salty diet can have profound effects on proteinuria levels. Thus, interpretation of the proteinuria results considering the clinical context is crucial. Quantitative thresholds for proteinuria are arbitrary; a glomerular proteinuria of less than 0.5 g proteinuria/day or 500 mg/g creatinine can still indicate a proliferative glomerulonephritis, when occurring in the context of an active urinary sediment and/or hypertension, whilst a tubular proteinuria above this threshold and without signs of nephritis may not. A nephrology consult is advisable for persistent proteinuria identified by any means in a patient with SLE. KDIGO also states that a decline in glomerular filtration rate (GFR), not attributable to a cause other than SLE, should trigger a kidney biopsy. Starting treatment for LN without a kidney biopsy should be restricted to patients where the risk of kidney biopsy outweighs the benefits, e.g. a high bleeding risk in patients on anticoagulants or with thrombocytopenia.

Treatment targets

EULAR/ERA and KDIGO refer to a proteinuria of <0.5–0.7 g/24 h at 12 months with GFR normalization/stabilization as a treatment target (Table 1), a threshold identified by a combined longitudinal analysis of major LN trials [6, 7]. KDIGO distinguishes a complete from a partial response. Both guidelines acknowledge that patients starting with nephrotic-range proteinuria may need more time to reach this threshold. However, a study documenting a delayed decline did not assess long-term outcome of these patients; hence, the prognostic relevance remains questionable [8]. Importantly, not reaching this threshold does not necessarily equate to a poor prognosis [6, 7], implying that even patients with ongoing, significant proteinuria may still benefit from immunosuppressive treatment if GFR is normalized or at least stable. That said, an inadequate response to induction therapy, with either decline in proteinuria within the first 6 months or significant persistent proteinuria together with persistent haematuria, remains a concern. It is an indication for further diagnostic assessment (drug adherence, causes for glomerular hyperfiltration such as a high salt intake, diabetes or obesity, genetic testing) and preferably a repeat biopsy to verify immunological disease activity within the kidney [9].

Table 1. Recommendations for the management of LN by EULAR/ERA 2019 and KDIGO 2021

Topic	EULAR/ERA-EDTA 2019 overarching principles/recommendations	KDIGO 2021 practice points/recommendations	Clinical impact of differences between the two guidelines
Indication for kidney biopsy	<ul style="list-style-type: none"> To be considered with persistent proteinuria ≥ 0.5 g/24 h (or UPCR ≥ 0.5 g/g in morning first void urine) and/or an unexplained decrease in GFR Kidney biopsy is indispensable and no other clinical or laboratory variables can substitute for it 	<p>Consider biopsy if either</p> <ul style="list-style-type: none"> Dipstick protein $\geq 2+$ (any level of specific gravity) or $1+$ if urine diluted or spot UPCR > 0.5, \pm sediment positive for acanthocytes ($\geq 5\%$), red blood cells or white blood cells, confirm proteinuria > 0.5 g/day in 24-h urine collection, OR eGFR < 60 mL/min/1.73 m² or decreasing if attributable to SLE 	
Kidney biopsy interpretation	ISN/RPS 2003 classification is recommended with additional assessment of activity and chronicity indices as well as of thrombotic and vascular lesions	Kidney biopsies should be read by an experienced kidney pathologist and classified according to the ISN/RPS scheme and EM (where available) and note features of activity and chronicity	
Treatment targets	<ul style="list-style-type: none"> Preservation (or improvement) of kidney function plus a reduction in proteinuria of $\leq 25\%$ by 3, $\leq 50\%$ by 6, a UPCR < 0.5–0.7 g/g by 12 months (nephrotic-range proteinuria at baseline by 18–24 months), keep therapy, if proteinuria is improving Additional target: remission or low-disease activity of extrarenal domains 	<ul style="list-style-type: none"> $\geq 25\%$ proteinuria reduction + normal complement at 2 months = good outcome predictor CRR within > 6–12 months: proteinuria reduction to < 0.5 g/g as UPCR from 24-h urine AND stabilization or improvement in kidney function (± 10–15% of baseline) PRR within 6–12 months: proteinuria reduction $> 50\%$ and < 3 g/g as UPCR from 24-h urine AND stabilization or improvement in kidney function (± 10–15% of baseline) OR < 0.7–0.8 g/24 h within 12 months 	
Hydroxychloroquine	<ul style="list-style-type: none"> For all patients without contraindication Max. 5 mg/kg/day adjusted for GFR 50% dose reduction in GFR < 30 mL/min Eye monitoring upon 5 years of therapy, then yearly or yearly from the start if risk factors (e.g. GFR < 30 mL/min) 	<ul style="list-style-type: none"> For all patients or an equivalent antimalarial unless contraindicated Initially 6.5 mg/ideal weight/day or 400 mg/day During maintenance 4–5 mg/kg/day $\geq 25\%$ dose reduction if eGFR < 30 mL/min/1.73 m² Baseline retinal exam and annually, especially after 5 years of use HCQ toxicity is a rare cause of persistent proteinuria in LN 	<p>Despite different ways of calculating the HCQ starting dose for most adults the maximal dose will not exceed 400 mg</p> <p>Several cases of HCQ toxicity with Fabry-like ‘zebra bodies’ in podocytes have been reported as a cause of persistent proteinuria in LN</p>
Therapy LN class I/II	<ul style="list-style-type: none"> No need for specific immunosuppression beyond treatment for extrarenal manifestations Repeat biopsy in significant proteinuria to detect class switch 	<ul style="list-style-type: none"> Low-level proteinuria: Immuno-suppressive treatment guided by extrarenal manifestations If nephrotic-range proteinuria (lupus podocytopathy), treat like MCD/FSGS: consider maintenance combination therapy with low-dose steroids and another immunosuppressive agent 	LN I/II plus nephrotic-range proteinuria is suggestive of a concomitant podocytopathy with a low threshold for proteinuria triggered even by a mild LN. May benefit from specific diagnostic work-up
Induction therapy active class III/IV ($\pm V$), steroids	IV pulses methylprednisolone (total dose 0.5–2.5 g, depending on disease severity) followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤ 7.5 mg/day by 3–6 months	<ul style="list-style-type: none"> Initial IV methylprednisolone 0.25–0.5 g/day for 1–3 days Oral prednisolone at start 0.6–1 mg/kg (max. 80 mg) tapering to < 5–7.5 mg/day over a few months If satisfactory improvement in kidney AND extrarenal disease to initial therapy, moderate-dose oral steroids (0.6–0.7 mg/kg to < 5 mg after week > 25) or reduced-dose oral steroids (0.5–0.6 mg/kg to < 2.5 mg after week > 25) can be considered 	Recent studies suggest that less oral steroids (lower starting dose and faster taper) can be as efficient as traditional doses

Table 1. Continued

Topic	EULAR/ERA-EDTA 2019 overarching principles/recommendations	KDIGO 2021 practice points/recommendations	Clinical impact of differences between the two guidelines
Induction therapy active class III/IV (\pm V)	MMF (2–3 g/day, or MPA at equivalent dose) or low-dose IV CYC (6 \times 0.5 g every 2 weeks)	<ul style="list-style-type: none"> • MMF (2–3 g/day) or MPA (1.44–2.16 g/day) for >6 months • Low-dose CYC IV (0.5 g/2 weeks for 6 doses) (efficacy data in mainly in Caucasians) • MMF/MPA is preferred in patients at risk of infertility, Asian, Hispanic, African ancestry or prior exposure to CYC • CYC preferred, if suboptimal adherence is anticipated 	Certain preferences apply to specific populations
Induction therapy active class III/IV (\pm V), alternatives	<ul style="list-style-type: none"> • In patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) consider high-dose IV CYC (0.5–0.75 g/m² monthly for 6 months) 	<ul style="list-style-type: none"> • Pulse IV CYC (0.5–1 g/m²) for 6 months (efficacy data in different ethnicities) • Oral CYC 1–1.5 mg/kg/day max. 150 mg for 2–6 months (efficacy data in different ethnicities) • Belimumab: can be added to standard therapy • RTX: consider for repeated flares • AZA (accepted in pregnancy) or leflunomide if patient intolerant, other unavailable or expensive) 	Recently, belimumab was approved by FDA and EMA for the initial treatment of active LN and further alternatives exist as listed by KDIGO
Induction therapy active class III/IV (\pm V), CNI + reduced dose MMF	MMF (1–2 g/day) or MPA at equivalent dose) with a CNI (especially TAC), particularly in nephrotic-range proteinuria	<ul style="list-style-type: none"> • Only, in patients not tolerating MPAA regimen or unfit for CYC or refuse CYC • Voclosporin (23.7 mg \times 2) can be added to MMF/MPA and steroids for 1 year in eGFR >45 mL/min/1.73 m² 	Previous trials exclusively from Asia with remaining concerns about rate of adverse effects and nephrotoxicity. Recently, voclosporin confirmed rapid and strong effect on proteinuria control in patients on MMF from all world regions with a GFR >45 mL/min/1.73 m ²
Maintenance therapy class III/IV (\pm V): steroids	<ul style="list-style-type: none"> • Low-dose prednisone (2.5–5 mg/day) when needed to control activity • Gradual withdrawal of steroids after \geq3–5 years therapy in complete clinical response 	<ul style="list-style-type: none"> • Taper to lowest possible dose except if required for extrarenal manifestations • Can consider to stop after CRR for \geq12 months 	
Maintenance therapy class III/IV (\pm V), first-line agents	<ul style="list-style-type: none"> • Upon improvement with initial treatment with MMF: MMF/MPA (dose: 1 to 2 g/day) • Upon improvement of initial treatment with CYC: MMF/MPA as before or AZA (2 mg/kg/day) • AZA is preferred if pregnancy is contemplated • Gradual withdrawal of MMF or AZA upon steroid withdrawal and \geq3–5 years therapy in complete clinical response • HCQ to be continued long term 	<ul style="list-style-type: none"> • MMF (1.5–2 g/day) or MPA (1080–1440 mg/day) (initial + maintenance therapy not <36 months in CRR and no extrarenal manifestations for >36 months) 	<ul style="list-style-type: none"> • EULAR/ERA considers MMF/MPA and AZA as equipotent after CYC induction based on the results of the MAINTAIN trial with European patients. The extended ALMS trial across all world regions found AZA inferior to MMF. Cytopenias were more common with AZA. AZA is less costly than MMF and has benefits if pregnancy is contemplated • A kidney biopsy can help the decision whether it is safe or not to stop therapy. In patients with residual LN activity therapy should be continued
Maintenance therapy class III/IV (\pm V), second-line agents	<ul style="list-style-type: none"> • AZA 2 mg/kg/day (particularly for pregnancy/cost) • Belimumab can be considered as add-on therapy to reduce extrarenal SLE activity and the risk for flares 	<ul style="list-style-type: none"> • AZA 1.5–2 mg/kg/day if intolerant/unavailable MMF/MPA or considering pregnancy • Alternatives: CNI (preferred if considering pregnancy) or mizoribine if MMF/MPA or AZA cannot be used • Caution when adding a CNI to reduce proteinuria (evidence of podocytopathy desirable) 	

Table 1. Continued

Topic	EULAR/ERA-EDTA 2019 overarching principles/recommendations	KDIGO 2021 practice points/recommendations	Clinical impact of differences between the two guidelines
Pure class V: indication immunosuppressive therapy	Immunosuppression plus steroids for nephrotic-range proteinuria or when UPCr exceeds 1 g/g despite the optimal use of RAS inhibitors	Only for nephrotic syndrome or nephrotic-range proteinuria or guided by extrarenal manifestations; consider immunosuppression if worsening of proteinuria and/or complications of proteinuria (thrombosis, oedema) under conservative therapy	
Induction therapy pure class V: first line	<ul style="list-style-type: none"> Initial IV methylprednisolone 0.5–2.5 g followed by oral prednisone 20 mg tapered to ≤5 mg by 3 months plus MMF 2–3 g/day or MPA at equivalent dose 	<ul style="list-style-type: none"> At low-level proteinuria: immunosuppression guided by extrarenal SLE, HCQ, RAAS inhibition At nephrotic-range proteinuria: combined immunosuppression with steroids AND MMF/MPA (reasonable first choice) or CYC (for <6 months) or CNI (if prior CYC or intolerant) or RTX (if prior CYC or intolerant) or AZA HCQ, RAAS inhibition 	The prognosis of pure class V depends on the level of proteinuria and the presence or absence of nephrotic syndrome
Induction therapy pure class V: second line	<ul style="list-style-type: none"> CYC CNI (especially TAC) monotherapy CNI + MMF/MPA in patients with nephrotic-range proteinuria 		
Maintenance therapy pure class V	Continuation, switching to or addition of CNIs (especially TAC) can be considered at the lowest effective dose and after considering nephrotoxicity risks		
Failure to achieve treatment goals/refractory disease	<ul style="list-style-type: none"> Thorough evaluation of the possible causes, including assessment of drug-adherence and therapeutic drug monitoring For active disease: switch to one of the alternative initial therapies or RTX (1 g on days 0 and 14) Mentioned: obinutuzumab, belimumab, IVIGs, plasma exchange (rarely indicated) 	<ul style="list-style-type: none"> Evaluate compliance and adequate dosing (drug levels) Repeat biopsy, if concern for chronicity/other diagnoses (TMA) Switch MMF/MPA to CYC, CYC to MMF/MPA If refractory, combine MMF/MPA + CNI OR add RTX (or another biologic agent) OR extend IV CYC Mentioned: obinutuzumab, belimumab 	Switching drugs makes sense only when drug non-adherence is an unlikely cause. There is little experience with belimumab as a rescue therapy of LN but it has benefits as early add-on to standard of care in active LN
Therapy of relapse		<ul style="list-style-type: none"> Use initial therapy that achieved original response or an alternative first-line agent 	In case of drug non-adherence or recent dose reductions recurrent active LN should respond again to the initial treatment
Follow-up screening	<ul style="list-style-type: none"> Visits every 2–4 weeks during first 2–4 months after diagnosis or flare, then according to response At each visit: body weight, BP, GFR, albumin, UPCr/24 h-U Urine red cell count or sediment and blood cell count if active nephritis aPL, C3/C4, anti-dsDNA periodically, anti-C1q, if available Repeat biopsy if: refractory, worsening, relapse 	<ul style="list-style-type: none"> Mind cumulative dose of CYC Visit frequency and tests not specified Repeat biopsy considered, if concerns for chronic damage or other diagnosis 	Follow-up intervals can be individualized depending on the response to therapy

Table 1. Continued

Topic	EULAR/ERA-EDTA 2019 overarching principles/recommendations	KDIGO 2021 practice points/recommendations	Clinical impact of differences between the two guidelines
Adjunctive therapies	<ul style="list-style-type: none"> • RAAS inhibition, if UPCr >0.5 g/g or arterial hypertension • BP target: <130/80 mmHg • Statin depending on CVRF-score • Avoid nephrotoxins (no NSAIDs) • Bone protection: general measures, Vit D/Ca/antiresorptives) • Vaccination: influenza, pneumococci, VZV (based on individual RF) • If aPL+, ASA (80–100 mg/day) after balancing benefits/bleeding risks • Anticoagulants considered if nephrotic syndrome with albumin <20 g/L 	<ul style="list-style-type: none"> • RAAS inhibition, BP control • BP target: <130/80 mmHg • Avoidance of high-sodium diet • Dislipidemia management • Bone protection: general measures Vit D/Ca/bisphosphonates when appropriate • Vaccination: influenza, pneumococci, HBV, VZV (based on individual RF) • Screening for HBV, HCV, HIV • <i>Pneumocystis jirovecii</i> prophylaxis Based on individual risk constellation • Contraception, gonadal preservation • Age-adjusted cancer screening • Limit CYC exposure to <36 g • Full anticoagulation in case of thrombotic events in nephrotic syndrome, prophylactic anticoagulation based on individual risk–benefit assessment 	The use of anticoagulants, pneumocystis prophylaxis, contraception and age-adjusted cancer screening are all important considerations. Risks for thromboembolism versus serious bleeding should be balanced for prophylactic anticoagulation in nephrotic syndrome
Pregnancy	<ul style="list-style-type: none"> • Planned in stable, inactive LN • Ideally UPCr <0.5 g/g for 6 months + GFR >50 mL/min • Compatible medications: HCQ, prednisone, AZA and/or CNIs (especially TAC) 3 to be continued at safe dosages (pregnancy/lactation) • Stop MMF and switch 3–6 months before pregnancy to test efficacy of new therapy • ASA to avoid pre-eclampsia • Controls every 4 weeks, preferably with experienced obstetrician • Flares treated with acceptable medications as stated above or IV pulses of MPA 	<ul style="list-style-type: none"> • Advise patients to avoid pregnancy if active LN OR treatment with teratogenic drugs is ongoing AND for ≥6 months after LN becomes inactive • HCQ continued (to reduce the risk of complications), start low-dose aspirin <16 weeks of gestation • Only steroids, HCQ, AZA and CNIs are considered safe • Low-dose ASA 	
Paediatric	<ul style="list-style-type: none"> • Diagnosis, management and monitoring similar to adults • Coordinated transition programme 	Paediatric patients are treated similar to adults but need to consider issues relevant to this population (dose adjustments, growth, fertility, psychological factors)	
Kidney failure	<ul style="list-style-type: none"> • All kidney replacement modalities can be used • Transplantation preferred after 6 months of clinically and ideally serologically inactive SLE • Outcomes better with living donation or pre-emptive Tx • HD and PD identical outcomes • Immunosuppressive therapy guided by extrarenal manifestations • aPL testing before transplantation 	<ul style="list-style-type: none"> • Transplantation is preferred to long-term dialysis, as soon as disease is quiescent • HD and PD similar outcomes • If aPL positive, consider prophylactic anticoagulation 	
Anti-phospholipid antibodies and TMA	<ul style="list-style-type: none"> • ASA may be used upon balancing risks in high-risk profiles • aPL-related nephropathy: ASA/anticoagulant can be considered + HCQ 	<ul style="list-style-type: none"> • TMA should be managed according to the underlying aetiology (TTP, aHUS, aPL-related nephropathy) • Long-term anticoagulants are reasonable to treat aPL-related nephropathy 	Presence of TMA in patients with SLE does not necessarily relate to aPL. It is reasonable to consider also other causes of TMA treatments are different for the various forms of TMA

ISN/RPS, International Society of Nephrology/Renal Pathology Society; MCD/FSGS, minimal change disease/focal segmental glomerulonephritis; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; EMA, European Medicines Agency; Tx, transplantation; TAC, tacrolimus; IVIG, intravenous immunoglobulin G therapy; BP, blood pressure; C3/C4, complement factor 3/4; NSAID, non-steroidal anti-inflammatory drug; CVRF, cardiovascular risk factor; Vit D, vitamin D; Ca, calcium; HBV/HCV, hepatitis B/C virus; HIV, human immunodeficiency virus; PJP, *Pneumocystis jirovecii* pneumonia; aPL, anti-phospholipid antibodies; TTP, thrombotic thrombocytopenic purpura; aHUS, atypical haemolytic-uremic syndrome; CRR, complete renal response; PRR, partial renal response.

Hydroxychloroquine

Despite different methods of calculation, the hydroxychloroquine (HCQ) starting dose will not exceed 400 mg for most adults (Table 1). In addition, the package insert mentions a starting dose of 400 mg. Most studies addressing the effects of HCQ consistently report that HCQ is safe and reduces flare rates and kidney events in LN [10, 11]. Both guidelines stress that in patients with CKD stage G4 dose reduction is necessary (Table 1). Neither package insert nor public dosing databases provide clear evidence as to how a decline in GFR affects HCQ blood levels. Essentially, in kidney failure it is unknown whether HCQ dose adjustment is necessary. One study reported a trend toward lower plasma levels of HCQ in patients with kidney failure [12], which implies that minor dose adjustment might be preferable in patients with CKD G4 or 5 unless additional risk factors or signs of HCQ toxicity suggest otherwise.

Finally, the two guidelines slightly differ on the recommended interval for ophthalmology screening for ocular HCQ complications (Table 1). Length of administration of more than 5 years, a total dose of more than 1000 g and a dose higher than 6.5 mg/kg daily, concomitant CKD and preexisting maculopathy are well recognized risk factors for ocular adverse events of HCQ therapy [13]. The vast majority of patients with LN will start therapy at an early stage of CKD and therefore starting annual check-ups after 5 years of HCQ treatment is probably safe [14]. However, starting HCQ therapy in patients with CKD G3 or below should prompt annual ophthalmology consults from the outset.

The KDIGO guidelines mention that several cases of HCQ toxicity as a cause of persistent proteinuria have been reported [5]. A hallmark ‘zebra bodies’ inside podocytes noted by electron microscopy is similar to the phospholipidosis in patients with M. Fabry [15].

Therapy LN class II

In contrast to EULAR/ERA, KDIGO specifies how to treat nephrotic-range proteinuria in the absence of proliferative LN when electron microscopy suggests a ‘lupus podocytopathy’ (Table 1). ‘Lupus podocytopathy’ is a recently introduced term describing patients with a selective injury to podocytes, clinically evident as nephrotic syndrome or nephrotic-range proteinuria, but which cannot be explained by LN alone, e.g. in class II LN. A ‘lupus podocytopathy’ implies concomitant co-factors of podocyte injury, which could be of humoral, genetic, toxic or of infectious origin similar to the non-SLE-related podocytopathies [16–18]. For example, apolipoprotein L1 (APOL-1) risk alleles reach a prevalence of 30% in people of West African origin and predispose to podocyte injury and accelerated CKD progression. APOL-1 risk allele-positive patients with SLE are prevalent in the USA and other areas of the world with populations of West-African origin [19, 20]. However, lupus podocytopathy together in the context of mesangial LN also occurs in other populations [21] and can respond well initially to steroids and immunosuppressive regimen used for other podocytopathies with minimal lesions

(‘minimal change disease’) [16, 18]. When lupus podocytopathy relapses after steroid taper, KDIGO proposes the use of low-dose steroids plus one of the available steroid-sparing agents [mycophenolic acid (MPA), azathioprine (AZA) or calcineurin inhibitors (CNI)]. Importantly, more recently rituximab (RTX) has also shown good results as a steroid-sparing agent in podocytopathies with minimal lesions. The aim of such treatments is to control proteinuria by suppressing the immune-mediated contribution to podocyte injury. In cases with proteinuria resistant to immunotherapy, a non-immune podocytopathy component may predominate [20].

Induction therapy class III/IV—steroids

The two guidelines agree on the indication of intravenous loading dose to suppress tissue inflammation inside the kidney quickly and to induce apoptosis in antigen presenting cells and lymphocytes involved in the autoimmune process outside the kidney [1, 22]. Due to a lack of studies that directly compare outcomes of different steroid dosing regimen, it is difficult to make clear recommendations (Table 1). Among the more recent clinical trials, there is a general trend towards both reducing the starting dose and accelerating the oral steroid taper within the first 3–6 months, with no observed reduction in efficacy compared with standard treatment regimens. This is of particular relevance to patients with obesity, diabetes and previous steroid toxicity, as well as to the paediatric population because of concerns about growth. Physicians have to balance the benefits and risks of steroid treatment on an individual basis.

Induction therapy class III/IV—first-line immunosuppression

The recommendations of the two guidelines regarding first-line immunosuppression are identical in terms of drug options and dosing; however, KDIGO suggests preferences for specific patient populations (Table 1). These refer to the results of the Aspreva Lupus Management Study and other clinical trials, which suggested better outcomes for either of the two drug options in certain ethnicities [23]. As a rule, intravenous treatment may be of value in patients in whom there are difficulties with adherence to oral medication.

Induction therapy class III/IV—alternative immunosuppression

Both guidelines list pulsed cyclophosphamide (CYC) for 6 months in aggressive forms of proliferative LN. In addition, KDIGO also lists oral CYC as an option for induction therapy (Table 1). Oral CYC offers several advantages over intravenous therapy including cost effectiveness, good efficacy and ease of administration [24, 25]. The latter is of particular relevance in countries with limited numbers of centres where patients may have to travel long distances. On the other hand, oral CYC may be associated with adverse events such as infection, infertility and late malignancies, all related to dose and/or total lifetime exposure >36 g [25]. Regardless, oral CYC may still

represent a valuable treatment option in specific patients and in the healthcare settings of certain countries. KDIGO lists other treatment options for induction therapy such as leflunomide or the combination of CNI plus low-dose MPA, probably because good evidence for these treatments has been reported for Chinese patients with LN and recently for voclosporin [26–28]. EULAR/ERA do not comment on these options, likely because similar data for European populations are not available. However, there could be useful options for Asian patients with LN living in Europe or patients with nephrotic-range proteinuria where adding a CNI may elicit specific anti-proteinuric effects at the filtration barrier of the kidney, if GFR is preserved [29]. Similarly, EULAR/ERA did not mention voclosporin as a potential induction therapy because the respective phase 3 trial results were not yet available at the time when the EULAR/ERA guidelines were released [28].

Maintenance therapy class III/IV—steroids

A recent randomized clinical trial confirmed that stopping the final 5 mg of oral prednisolone in patients with a minimum of 1 year of clinically quiescent disease increased the risk for a lupus flare by 4-fold [30]. Thus, both guidelines suggest gradually tapering the maintenance dose of oral steroid to the lowest possible dose, which includes a possible withdrawal of steroids after a considerable period of complete clinical remission. No studies have compared different periods of complete clinical remission before ultimate steroid withdrawal.

Maintenance therapy class III/IV—first-line immunosuppression

EULAR/ERA considers mycophenolate mofetil (MMF)/MPA and AZA as equipotent after CYC induction based on the results of the MAINTAIN trial with European patients [31]. The extended ALMS trial across all world regions found AZA inferior to MMF [32]. Cytopenias were more common with AZA [32]. The EULAR/ERA guideline advises against tapering first-line immunosuppressive agents before 5–6 years of complete kidney response, whilst KDIGO states, ‘the total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be less than 36 months’ (Table 1). EULAR/ERA argue, ‘Most of the kidney flares occur within the first 5–6 years following treatment initiation’, a finding largely based on cohorts of European patients [31, 33–35]. However, no clinical trial has ever compared flare rates between these two approaches. In clinical practice, personal preferences, drug tolerance, immune parameters, extrarenal SLE activity, results of a repeat biopsy and other individual factors, in particular the desire to become pregnant, will contribute to the decision for the duration of maintenance therapy.

Maintenance therapy class III/IV—alternative immunosuppression

Various second-line drug options are available for maintenance therapy. Both KDIGO and EULAR/ERA name be-

limumab. The BLISS-LN trial suggests that belimumab can reduce SLE disease activity and prevent flares and hence progression of CKD in LN [36, 37]. Finally, KDIGO mentions utilizing CNIs for patients with persistent proteinuria for the same reasons mentioned previously [29].

Induction therapy class V—second-line therapy

Both guidelines name the same single drug options, but EULAR/ERA also lists CYC and CNI (tacrolimus), each in combination with steroids, providing two references that report results from Chinese patients [38, 39]. These results cannot be extrapolated to European patients with LN; hence, more data are needed to support this recommendation. The EULAR/ERA guideline does not reference the comment on the possible use of a combination of CNI plus MMF in class V LN. Indeed, data on this combination mostly refer to class IV/V, but data on pure class V LN are scarce [40].

Failure to achieve treatment goals/refractory LN

Many patients do not achieve the treatment goals, frequently referred to as ‘lack of response’ or ‘refractory LN’. Both guidelines are consistent in naming drug non-adherence as an important differential diagnosis and in advocating a measurement of plasma drug levels when available and a repeat biopsy to clarify immunological disease activity. For patients with persistently active LN, despite exposure to adequate doses of first-line therapies, both guidelines provide a list of possible rescue therapies including RTX, belimumab and obinutuzumab for which randomized trials document some efficacy, even if not specifically for second-line use (Table 1). As no comparative data in refractory LN exist, physicians can choose from the available options following individual, regional, ethnic and economical preferences. No randomized trial evidence is available for intravenous immunoglobulins and plasma exchange, and EULAR/ERA refers to these options based on uncontrolled single-centre studies in patients with SLE with or without LN [41, 42].

Therapy of relapse

Only KDIGO discusses how to treat recurrent LN and recommends the same therapy as in the first episode. However, they also highlight the risk of cumulative CYC exposure and note that to restrict this, consideration might be given to substituting the first-line agent (Table 1). Proteinuric or nephritic flares are not infrequent in LN, thus providing guidance seems reasonable. No recommendations address the timing of repeat flare biopsy depending on the previous class of LN, nor the context of extrarenal manifestations of a flare, or considering drug non-adherence whenever flares occur or the possibility of concomitant (kidney) diseases mimicking a LN flare, e.g. infections, including COVID-19 [43].

Follow-up screening

EULAR/ERA, but not KDIGO, sets clear visit intervals and test parameters for the first months of induction therapy,

probably because EULAR had published a previous consensus document on lupus patient monitoring [44]. However, no studies have compared the outcome of different follow-up intervals, and therefore these suggestions rather provide general advice that needs to be individualized based on the local settings and the individual patient. KDIGO did not provide guidance here, probably better accounting for the diversity of healthcare systems around the world. Nevertheless, it goes without saying that monitoring patients closely for adverse drug effects, response and patient education is paramount in this phase of the disease.

Adjunctive therapies

Both guidelines make consistent recommendations for most of the adjunctive therapies, particularly the use of renin-angiotensin-aldosterone (RAAS) inhibitors. However, CKD therapy should be rather considered a central strategy to improve kidney and cardiovascular outcomes in patients with LN rather than 'adjunct'. Neither guideline comments on the potential use of inhibitors of the sodium-glucose transporter-2 for the attenuation of CKD progression in patients with LN, probably due to the current lack of data in this specific patient group. Only KDIGO specifies testing for hepatitis B and C and human immunodeficiency virus (HIV). This again may reflect the global perspective of KDIGO and referring to parts of the world where these infections are important and common comorbidities in patients with LN that must be considered when choosing and dosing immunosuppressive medications. KDIGO also mentions prophylaxis for *Pneumocystis jirovecii* pneumonia based on individual risk factors, contraception, preservation of gonads with certain treatments and cancer screening, all important adjunctive measures to address in patients treated with immunosuppressive drugs.

Pregnancy

As LN is a disease of mostly women during fertile years, advice on fertility- and pregnancy-related issues is important during the different phases of disease management. Exposure to potentially teratogenic drugs (CYC, MPA, RAAS inhibitors, etc.) is difficult to avoid in patients with active disease, but pregnancy outcome is also poor in untreated active patients [1, 45]. The two guidelines provide somewhat different levels of detail regarding guiding women with LN through pregnancy. They do, however, agree about which drugs to avoid and which are preferable, including low-dose acetylsalicylic acid (ASA) prophylaxis against pre-eclampsia. Neither guideline specifies particular risks for pregnancy complications associated with the presence of anti-Ro and anti-phospholipid antibodies and concomitant risk factors for pre-eclampsia such as obesity, stage of CKD and level of proteinuria. EULAR/ERA recommends to counsel pregnant women with LN together with an experienced obstetrician, which, of course, may not be feasible in all healthcare settings.

Kidney failure

EULAR/ERA and KDIGO are consistent in naming kidney transplantation as the preferred route of kidney replacement therapy for patients with kidney failure (Table 1). EULAR/ERA adds a comment that the immunosuppressive therapy should be tailored by the extrarenal manifestations of SLE, probably representing the perspective of the participating rheumatologists. Frequently, advanced CKD and uraemia, themselves, represent an immunosuppressive state, which suppresses SLE activity, and the immunosuppressive drug regime employed for kidney transplantation usually sufficiently controls extrarenal SLE. However, some transplanted patients may still present with SLE flares and require additional immunosuppression to control SLE.

Thrombotic microangiopathy in SLE

Only the KDIGO guideline expands upon the different forms of thrombotic microangiopathy (TMA) that may occur in SLE and indicates a diagnostic algorithm to identify them [5]. We agree that the differential diagnosis of the various forms of TMA is important because each requires a different treatment [46]. Both guidelines acknowledge that the presence of anti-phospholipid antibodies may affect the natural course of LN [47], especially when presenting as a TMA (also referred to as anti-phospholipid antibody-related nephropathy) [48, 49]. Both guidelines express that the therapeutic relevance of anticoagulants is contentious in patients with LN and clinically asymptomatic presence of antiphospholipid antibodies.

CONCLUSIONS

The two new guidelines on the management of LN are timely and offer important support for physicians across different disciplines who provide care for patients with LN. Together they present largely consistent recommendations regarding when to use which drugs based on important randomized trials, which have provided the necessary scientific evidence for these aspects of LN management. The discrepancies between the guidelines refer mostly to aspects of management where evidence is lacking and in relation to the different practices for reviewing the available scientific evidence as well as the expertise and priorities of the experts involved in preparing the recommendations. Some of the differences may also relate to the input of 50% rheumatologists among the exclusively European panellists of EULAR/ERA, whereas KDIGO provides recommendations, based on a global panel of mostly nephrologists, recognizing data from all world regions and acknowledging that healthcare resources are not always comparable throughout the world. The rheumatologist perspective is also valuable for nephrologists and of course, there are non-Europeans with LN who reside in Europe, and thus they will benefit from the recommendations set out in the KDIGO guideline.

We hope that this clarifies the inconsistencies between the two guidelines and will be helpful in assisting physicians all

over the world to combine the best from both documents to optimize care of patients with LN.

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CONFLICT OF INTEREST STATEMENT

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