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

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Handling editor David S Pisetsky

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2020-216924).

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Received 1 January 2020
Revised 16 March 2020
Accepted 17 March 2020
Published Online First 27 March 2020

To cite: Fanouriakis A, Kostopoulou M, Cheema K, *et al*. *Ann Rheum Dis* 2020;**79**:713–723.

ABSTRACT

Objective To update the 2012 EULAR/ERA–EDTA recommendations for the management of lupus nephritis (LN).

Methods Following the EULAR standardised operating procedures, a systematic literature review was performed. Members of a multidisciplinary Task Force voted independently on their level of agreeement with the formed statements.

Results The changes include recommendations for treatment targets, use of glucocorticoids and calcineurin inhibitors (CNIs) and management of end-stage kidney disease (ESKD). The target of therapy is complete response (proteinuria <0.5–0.7 g/24 hours with (near-) normal glomerular filtration rate) by 12 months, but this can be extended in patients with baseline nephrotic-range proteinuria. Hydroxychloroquine is recommended with regular ophthalmological monitoring. In active proliferative LN, initial (induction) treatment with mycophenolate mofetil (MMF 2–3 g/day or mycophenolic acid (MPA) at equivalent dose) or low-dose intravenous cyclophosphamide (CY; 500 mg × 6 biweekly doses), both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone 0.3–0.5 mg/kg/day) is recommended. MMF/CNI (especially tacrolimus) combination and high-dose CY are alternatives, for patients with nephrotic-range proteinuria and adverse prognostic factors. Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no or low-dose (<7.5 mg/day) glucocorticoids. The choice of agent depends on the initial regimen and plans for pregnancy. In non-responding disease, switch of induction regimens or rituximab are recommended. In pure membranous LN with nephrotic-range proteinuria or proteinuria >1 g/24 hours despite renin–angiotensin–aldosterone blockade, MMF in combination with glucocorticoids is preferred. Assessment for kidney and extra-renal disease activity, and management of comorbidities is lifelong with repeat kidney biopsy in cases of incomplete response or nephritic flares. In ESKD, transplantation is the preferred kidney replacement option with immunosuppression guided by transplant protocols and/or extra-renal manifestations. Treatment of LN in children follows the same principles as adult disease.

Conclusions We have updated the EULAR recommendations for the management of LN to facilitate homogenization of patient care.

INTRODUCTION

Up to 40% of patients with systemic lupus erythematosus (SLE) develop kidney disease, which represents a major cause of morbidity.[1–3] In 2012, the European League Against Rheumatism–European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) developed joint recommendations for lupus nephritis (LN),[4] involving a panel of rheumatologists, nephrologists, renal pathologists and paediatricians. Since then, new evidence has emerged, which includes the use of calcineurin inhibitors (CNIs) and 'multitarget' therapy, disease monitoring and treatment targets. We therefore sought to update the recommendations for the management of LN.

METHODS

Following approval by the EULAR and ERA/EDTA Executive Committees, the convenors (DTB, DJ) invited a multidisciplinary panel of 11 rheumatologists, 11 nephrologists, 1 nephropathologist, 1 paediatric rheumatologist, 1 paediatric nephrologist, 1 allied health professional and 2 patient representatives. The EULAR standardised operating procedures[5] were followed and the Appraisal of Guidelines Research and Evaluation instrument was employed.[6] Delphi-based methodology led to

Table 1 Questions to be addressed by the SLR and final number of articles included

Diagnosis and classification of LN	Total number of articles included
1. What is the prognostic significance of kidney biopsy findings?	33
2. Risk stratification of patients with LN by incorporating demographic, clinical and histological data	64
Pharmacological treatment of LN	
3. What is the evidence for the benefits and harms of HCQ in LN?	16
4. 'Induction' therapies in LN (including dosage of glucocorticoids and use of CNIs)	127
5. 'Maintenance' therapies in LN (including dosage of glucocorticoids, and use of CNIs)	
Monitoring and therapeutic targets	
6. How should LN be monitored?	85
7. What is the goal of treatment in LN?	18
8. Duration of immunosuppressive treatment in LN	16
Refractory LN	
9. What is the definition of refractory LN?	13
10.How should refractory/flaring LN be treated?	36
Special topics in LN	
11.Management of LN during pregnancy and lactation	17
12.Management of antiphospholipid syndrome nephropathy	18
Chronic kidney disease in LN	
13.Management of end-stage renal disease in LN	42
14. Renal transplantation in patients with LN	44
Comorbidities and adjunct therapy in LN	
15.Comorbidities in LN (cardiovascular, infections)	49

The number of included studies refers to studies published after January 2012. The final LoE and GoRs considered the total body of evidence, including the 2012 recommendations for LN.
CNIs, calcineurin inhibitors; GoRs, grading of recommendations; HCQ, hydroxychloroquine; LN, lupus nephritis; LoE, level of evidence; SLR, systematic literature review.

15 questions for systematic literature review (SLR), which was undertaken by three fellows (AF, MK, KC; table 1). PubMed was searched using specific index terms and retrieved items were evaluated based on the title, abstract and/or full text. Since this is an update of the 2012 recommendations, we considered all English-language publications between January 2012 and December 2018. The total number of articles included are shown in table 1.

The results of the literature search were summarised, distributed to all members, presented and discussed on, during the meeting of the panel in May 2019. The previous recommendations[4] were reappraised and revised accordingly. The final level of evidence (LoE; scale: 1–4) and grading of recommendations (GoRs; scale: A (highest) to D (lowest)), according to the Oxford Centre for Evidence Based Medicine definitions,[7] (online supplementary table 1) considered the total body of evidence. Each member of the panel was then asked to rate their level of agreement (LoA) for each statement on a 0–10 rating scale (10 being full agreement), based on both the research evidence presented and their own clinical expertise. For the final voting, Task Force members had the 'opportunity' to express their potential disagreement for a particular statement, however omission of statements with less consensus was not considered necessary. The methods and results of the SLR will be published separately.

RESULTS

The overarching principles and specific recommendations, with the respective LoE, GoR and LoA, are listed in table 2.

Overarching principles

Despite an improved prognosis over the last decades,[8] LN poses therapeutic challenges and is linked to increased morbidity, mortality and healthcare costs. The nature of the disease (involvement of the kidneys in the context of a systemic autoimmune disease) mandates a multidisciplinary approach by rheumatologists and nephrologists, following histological confirmation and assessment of LN by a nephropathologist. In this regard, management or periodic evaluation of these patients in centres with expertise is recommended. Decision-making requires that the patient is adequately informed about the nature and natural course of the disease and the therapeutic options.

Recommendations

Investigation of the patient with suspected LN

Patients with SLE with any sign of kidney involvement (glomerular haematuria and/or cellular casts, proteinuria >0.5 g/24 hours (or spot urine protein-to-creatine ratio (UPCR) >500 mg/g), unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy. Mild clinical presentations (eg, subnephrotic proteinuria) can nonetheless be associated with active histological lesions.[9–11] In a review of kidney biopsies performed during 1970–2016, earlier use of biopsy based on urinary abnormalities, as done from 2001 to 2016, was associated with improved outcomes, despite similar rates of severe histology.[12] The benefits of histological evaluation should be balanced against increased bleeding risk in selected patients such as those receiving anticoagulation. All patients with SLE, especially those with suspected kidney involvement, should be tested for antiphospholipid antibodies (aPL), since renal manifestations of antiphospholipid syndrome, such as thrombotic microangiopathy (TMA), may carry prognostic implications. Testing for anti-dsDNA and anti-C1q (whenever available) autoantibodies should be considered in patients with suspected LN, along with complement levels (C3 and C4).[13]

Pathological assessment of kidney biopsy

The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification still represents the gold standard for assessment of kidney biopsy in LN (online supplementary table 2).[14] TMA lesions, although not pathognomonic, should raise suspicion of antiphospholipid syndrome nephropathy and thus, prompt aPL (re-)testing. Although TMA has been reported in up to 25% of LN biopsies,[15 16] its prognostic implications remain unclear.[17 18] Tubulointerstitial lesions, such as interstitial fibrosis and tubular atrophy, are associated with poor outcome.[19–21] A revision of the 2003 ISN/RPS classification has recently been proposed and awaits endorsement.[22]

Indications of immunosuppressive treatment in LN

Immunosuppressive treatment is recommended in active class III or IV LN, with or without coexisting histological chronicity. For pure class V LN, the recommendation for immunosuppression pertains to patients with nephrotic-range proteinuria, which is associated with worse prognosis, in addition to cases with proteinuria >1 g/24 hours despite optimal use of renin–angiotensin–aldosterone system blockers for a reasonable time period (eg, at least 3 months). Class II LN usually does not need specific immunosuppressive therapy, but may be prone to histological

Table 2 Overarching principles and recommendations for the management of patients with LN

Overarching principles		
Kidney involvement in SLE, a major cause of morbidity and mortality that leads to high medical and societal costs, is best managed by interdisciplinary care with shared patient–physician decisions.		
Vigilance for symptoms and signs suggestive of kidney involvement, histological assessment by nephropathologists and input from specialised centres ensure optimal outcomes.		
Goals of treatment include patient survival, long-term preservation of kidney function, prevention of disease flares, prevention of organ damage, management of comorbidities and improvement in disease-related quality of life.		
Management of active phases of LN includes an initial period of intense immunosuppressive therapy to control disease activity, followed by a longer period of usually less intensive therapy to consolidate response and prevent relapses.		
Recommendation/statement	**LoE/GoR**	**LoA, mean (SD)**
1. Investigation of the patient with suspected LN		
1.1 Kidney biopsy should be considered when there is evidence of kidney involvement, especially in the presence of persistent proteinuria ≥0.5 g/24 hours (or UPCR ≥500 mg/g in morning first void urine),	**2b/B**	**9.84 (0.54)**
and/or an unexplained decrease in GFR.	**2b/C**	
1.2 Kidney biopsy remains indispensable and its diagnostic and prognostic value cannot be substituted by other clinical or laboratory variables.	**2b/B**	**9.96 (0.20)**
2. Pathological assessment of kidney biopsy		
2.1 The use of the International Society of Nephrology/Renal Pathology SocietyISN/RPS 2003 classification system is recommended,	**2a/B**	**9.56 (0.94)**
with additional assessment of activity and chronicity indices,	**1b/A**	
as well as of thrombotic and vascular lesions associated with aPL/syndrome.	**2b/C**	
3. Indications for immunosuppressive treatment		
3.1 Immunosuppressive agents, administered in combination with glucocorticoids, are recommended in class III_A or $III_{A/C}$ (±V) and IV_A or $IV_{A/C}$ (±V) nephritis.	**1a/A**	**9.96 (0.20)**
3.2 In pure class V nephritis, glucocorticoids and immunosuppression are recommended in cases of nephrotic-range proteinuria,	**2b/B**	**9.04 (1.80)**
or when UPCR exceeds 1000 mg/g despite the optimal use of renin–angiotensin–aldosterone system blockers.	**5/D**	
4. Treatment of adult LN		
Goals of treatment		
4.1 Treatment aims for optimisation (preservation or improvement) of kidney function, accompanied by a reduction in proteinuria of at least 25% by 3 months,	**2b/D**	
50% by 6 months,	**2a/B**	**9.60 (0.63)**
and a UPCR target below 500–700 mg/g by 12 months (*complete clinical response*).	**2a/B**	
4.2 Patients with nephrotic-range proteinuria at baseline may require an additional 6–12 months to reach *complete clinical response*; in such cases, prompt switches of therapy are not necessary if proteinuria is improving.	**2a/C**	**9.68 (0.68)**
Initial treatment		
4.3 For patients with class III or IV (±V) LN, MMF(target dose: 2 to 3 g/day, or MPA at equivalent dose)	**1a/A**	**9.84 (0.37)**
or low-dose intravenous CY (500 mg every 2 weeks for a total of 6 doses)	**1a/A**	
in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.		
4.4 Combination of MMF (target dose: 1 to 2 g/day, or MPA at equivalent dose) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria.	**1a/B**	**9.32 (0.93)**
4.5 Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in 4.3–4.4,	**2b/B**	**8.88 (1.56)**
but high-dose ntravenous CY (0.5–0.75 g/m^2 monthly for 6 months) can also be considered.	**1a/B**	
4.6 To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months.	**2b/C**	**9.48 (0.90)**
4.7 In pure class V nephritis, MMF (target dose 2 to 3 g/day; or MPA at equivalent dose),	**2a/B**	
in combination with pulse intravenous methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months)	**2b/C**	**9.28 (0.96)**
is recommended as initial treatment due to best efficacy/toxicity ratio.		
4.8 Alternative options for class V nephritis include intravenous CY,	**2b/B**	**9.28 (0.92)**
or CNIs (especially TAC) in monotherapy	**2b/B**	
or in combination with MMF/MPA, particularly in patients with nephrotic-range proteinuria.	**1b/B**	
4.9 HCQ should be coadministered,	**2a/B**	**9.28 (1.40)**
at a dose not to exceed 5 mg/kg/day and adjusted for the GFR.	**3b/C**	
Subsequent treatment		
4.10 If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF/MPA (dose: 1 to 2 g/day)—especially if it was used as initial treatment—	**1a/A**	**9.80 (0.49)**
or AZA (2 mg/kg/day)—preferred if pregnancy is contemplated—in combination with low-dose prednisone (2.5–5 mg/day) when needed to control disease activity.	**1a/A**	
4.11 Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in *complete clinical response*. HCQ should be continued long-term.	**2b/C**	**9.40 (0.75)**

Continued

Table 2 Continued

Overarching principles		
4.12 Continuation, switching to or addition of CNIs (especially TAC) can be considered in pure class V nephritis at the lowest effective dose and after considering nephrotoxicity risks.	**2b/B**	**9.28 (1.15)**
Non-responding/refractory disease		
4.13 In case of failure to achieve the treatment goals, thorough evaluation of the possible causes is recommended, including assessment of adherence to treatment and therapeutic drug monitoring.	**5/D**	**9.84 (0.46)**
4.14 For active non-responding/refractory disease, treatment may be switched to one of the alternative initial therapies mentioned above,	**2b/B–C**	**9.64 (0.62)**
or RTX (1000 mg on days 0 and 14) may be given.	**2b/C**	
5. Adjunct treatment		
5.1 Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended for all patients with UPCR >500 mg/g or arterial hypertension.	**5/D**	**9.84 (0.37)**
5.2 Statins are recommended on the basis of lipid levels and estimated 10-year cardiovascular disease risk using the Systematic Coronary Risk Evaluation or other validated tools.	**5/D**	**9.52 (0.75)**
5.3 Bone protection (calcium/vitamin D supplementation and/or antiresorptive agents) and immunizations with non-live vaccines may reduce treatment-related and disease-related comorbidities and are recommended.	**5/D**	**9.68 (0.61)**
5.4 If aPL (defined as in the international consensus statement for definite antiphospholipid syndrome classification criteria) are positive, and based on aPL profile, acetyl-salicylic acid (80–100 mg/day) may be used after balancing benefits and bleeding risk.	**2a/C**	**9.28 (1.25)**
5.5 Anticoagulant treatment should be considered in cases of nephrotic syndrome with serum albumin <20 g/L.	**5/D**	**9.76 (0.43)**
5.6 Belimumab may be considered as add-on treatment, to facilitate glucocorticoid sparing, control extra-renal lupus activity and decrease the risk for extra-renal flares.	**2a/C**	**8.48 (1.92)**
6. Monitoring and prognosis of LN		
6.1 Visits should be scheduled every 2–4 weeks during the first 2–4 months after diagnosis or flare, and subsequently, according to response to treatment. Monitoring for renal, extra-renal disease activity and comorbidities is lifelong.	**5/D**	**9.40 (0.69)**
6.2 At each visit, body weight, blood pressure (including out-of-office measures), estimated GFR, serum albumin, proteinuria (UPCR or 24 hours urine collection), urine red cell count or sediment and complete blood cell count should be evaluated when nephritis is active and less frequently if stable.	**2b/B**	**9.64 (0.69)**
Serum C3/C4 and anti-dsDNA antibody levels are monitored periodically.	**2b/C**	
6.3 Repeat kidney biopsy should be considered in selected cases, such as worsening of kidney variables, non-responsiveness to immunosuppressive or biologic treatment (as defined above); or at relapse, to demonstrate possible histologic class transition or change in chronicity and activity indices; to provide prognostic information; and detect other pathologies.	**2b/B**	**9.84 (0.37)**
7. Management of ESKD in LN		
7.1 All methods of kidney replacement treatment can be used in patients with SLE.	**2b/B**	**9.96 (0.20)**
7.2 Immunosuppression in ESKD on dialysis should be guided by extra-renal manifestations.	**2b/C**	**9.76 (0.59)**
7.3 Transplantation may be preferred over other kidney replacement options and should be considered when extra-renal lupus is clinically (and ideally, serologically) inactive for at least 6 months; outcomes are better with living donor and pre-emptive transplantation.	**2b/C**	**9.84 (0.37)**
7.4 aPLs should be measured during transplant preparation, because they are associated with an increased risk of vascular events in the transplanted kidney.	**2b/C**	**9.48 (1.10)**
8. Antiphospholipid syndrome and LN		
8.1 In patients with antiphospholipid syndrome-associated nephropathy, antiplatelet/anticoagulant treatment can be considered, in addition to HCQ.	**2b/C**	**9.68 (0.55)**
9. LN and pregnancy		
9.1 Pregnancy may be planned in stable patients with inactive LN.	**1b/A**	**9.56 (0.80)**
Optimally, UPCR should be below 500 mg/g for the preceding 6 months, with GFR >50 mL/min.	**2b/C**	
9.2 Compatible medications such as HCQ,	**1b/B**	**9.76 (0.51)**
prednisone, AZA and/or CNIs (especially TAC)	**3b/C** for all	
should be continued at safe dosages throughout pregnancy and lactation.		
9.3 MMF/MPA should be withdrawn at least 3–6 months before conception is planned, to ensure that an alternative immunosuppressive agent does not lead to a relapse.	**5/D**	**9.29 (0.93)**
9.4 During pregnancy, acetylsalicylic acid is recommended to reduce the risk of pre-eclampsia.	**2b/C**	**9.64 (0.62)**
9.5 Patients should be assessed at least every 4 weeks, preferably by a multidisciplinary team including an obstetrician with expertise in the disease.	**5/D**	**9.56 (0.80)**
9.6 Flares of LN during pregnancy can be treated with acceptable medications stated above and pulses of intravenous MPA, depending on flare severity.	**3b/C**	**9.56 (1.39)**
10.Management of paediatric patients		
10.1 LN in children is more common at presentation and more severe with increased damage accrual; the diagnosis, management and monitoring are similar to that of adults.	**3b/C**	**9.68 (0.68)**
10.2 A coordinated transition programme to adult specialists is essential to ensure adherence to therapy and optimisation of long-term outcomes.	**5/D**	**9.84 (0.37)**

The LoE, GoR and final LoA are shown in bold for each recommendation.
aPL, antiphospholipid antibodies; AZA, azathioprine; CNI, calcineurin inhibitor; CY, cyclophosphamide; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GoR, grading of recommendation; HCQ, hydroxychloroquine; ISN/RPS, International Society of Nephrology/Renal Pathology Society; LN, lupus nephritis; LoA, level of agreement; LoE, level of evidence; MMF, mycophenolate mofetil; MPA, mycophenolic acid; RTX, rituximab; SLE, systemic lupus erythematosus; TAC, tacrolimus; UPCR, urine protein–creatine ratio.

transformation to more aggressive disease on repeat biopsy. The presence of significant proteinuria should prompt histological reassessment for detection of proliferative changes that may have been overlooked.

Treatment of adult LN

Goals of treatment

Compared with the previous recommendations, the goals of treatment were further defined according to time since treatment initiation. Post hoc analyses from the MAINTAIN and Euro-Lupus Nephritis Trials suggest that proteinuria at 12 months represents the best single predictor for long-term renal outcome (ie, risk for end-stage kidney disease (ESKD) or doubling of serum creatine after 10 years).[23–27] Accordingly, therapy should aim for proteinuria <0.5–0.7 g/24 hours by 12 months (*complete clinical response*), although up to 50% of patients not reaching this milestone may still have stable long-term kidney function.[25 28] Evidence of improvement in proteinuria (with GFR normalisation/stabilisation) should be noted by 3 months,[29 30] and at least 50% reduction in proteinuria (*partial clinical response*) by 6 months. For patients with nephrotic-range proteinuria at baseline, the aforementioned time frames may be extended by 6–12 months, due to slower proteinuria recovery.[31] Thus, consideration of decreasing proteinuria can avoid premature treatment changes. Since SLE is a systemic disease, immunosuppressive therapy should also target remission or low disease activity from extra-renal domains.[32]

Initial treatment

In class III-IV LN, an updated Cochrane systematic review suggested similar efficacy of mycophenolate mofetil/mycophenolate acid (MMF/MPA) compared with cyclophosphamide (CY),[33] with possible ethnic/racial differences, that is, MMF potentially being more efficacious in African–Americans.[34] The 10-year Euro-Lupus Nephritis Trial data showed equal efficacy of low-dose versus high-dose CY,[24] and the low-dose regimen has been used in non-European populations.[35–38] Consequently, both MMF/MPA and low-dose CY are recommended as *first-line* options for initial (*induction*) treatment. The recommended target dose of MMF is now changed to 2–3 g/day (MPA 1.44–2.16 g/day), based on evidence that therapeutic drug dosage may range between 1 and 3 g/day. Dose may be adjusted according to tolerance/adverse effects, efficacy and trough MPA blood levels. High-dose intravenous CY (0.5–0.75 g/m^2 monthly for 6 months) can be considered in patients with adverse clinical (nephritic urine sediment and impaired renal function with GFR between 25 and 80 mL/min) or histological (crescents or necrosis in >25% of glomeruli) prognostic factors.[39]

The realisation of the adverse effects of long-term glucocorticoid treatment, together with emerging evidence that following initial pulse intravenous methylprednisolone, lower starting dose of glucocorticoids (≤0.5 mg/kg/day) may be as efficacious as higher dose,[40–42] led the Task Force to recommend that total intravenous methylprednisolone dose may range from 500 to 2500 mg (allowing flexible dosing depending on disease severity), and starting oral prednisone dose may be 0.3–0.5 mg/kg/day, reducing to ≤7.5 mg/day by 3–6 months.

Focus has been placed on the use of calcineurin inhibitors (CNIs, tacrolimus (TAC) and cyclosporine A (CsA)), either as a monotherapy or in combination with MMF/MPA.[43–46] A randomised controlled trial (RCT) in 362 Chinese patients found the combination of TAC/MMF to be superior to CY in the short-term.[47] In a phase II RCT, a cyclosporine analogue, voclosporin when combined with MMF was associated with a higher frequency of complete response at 6 months as compared with MMF alone, although more side effects and deaths occurred in the former group.[42] A number of meta-analyses suggest that CNI (alone or as part of multitarget regimen) may have favourable efficacy/toxicity ratio in LN,[48] and thus, in a new statement (4.4), the combination of MMF with a CNI (especially TAC) is included as therapeutic option, particularly in cases with nephrotic-range proteinuria. Until more data in non-Asian populations and studies with longer follow-up and on renal outcomes such as prevention of kidney insufficiency/failure are available, CNI and the 'multitarget' regimen cannot be universally recommended as first-line treatment. Additionally, nephrotoxicity and other side effects of CNI use should be considered when opting for a CNI-based regimen.

In pure class V LN, no high-quality evidence has emerged over the last 7 years. MMF/MPA is recommended as first-choice at the same doses as in class III/IV disease. CY and CNI (especially TAC), the latter as monotherapy or combined with MMF, are alternative options.[43 49] Similar to class III/IV LN, rituximab (RTX) is reserved for non-responders in class V LN (see below), although a recent RCT in idiopathic membranous nephropathy, which demonstrated short-term superiority over CsA, may justify a modification once similar data emerge in LN.[50]

Hydroxychloroquine (HCQ) is recommended for all patients with LN, in the absence of contraindications. HCQ use is linked to reduced risk of kidney flares, ESKD and death.[51–55] In light of emerging data regarding ocular toxicity with more sensitive screening techniques, and in accordance to a revised statement by the American Academy of Ophthalmology, daily HCQ dose should not exceed 5 mg/kg actual body weight and should be continued indefinitely with regular ophthalmological screening (after 5 years on HCQ and yearly thereafter, or yearly from baseline in the presence of risk factors).[32 56] Dose adjustments (50% reduction) and yearly eye monitoring from onset are recommended for patients with GFR <30 mL/min.

Subsequent treatment

MMF/MPA and azathioprine (AZA) remain the drugs of choice for subsequent immunosuppressive treatment, following adequate response during the initial phase. The two regimens did not differ in terms of kidney flares in the 10-year follow-up of the MAINTAIN Trial,[24] in contrast to the Aspreva Lupus Management Study (ALMS) which showed superiority of MMF.[56] Based on evidence showing increased relapses when MMF/MPA is followed by AZA,[57 58] we recommend MMF/MPA induction to be followed by MMF/MPA maintenance. CY induction can be followed by either MMF/MPA or AZA; the latter agent is preferred if pregnancy is contemplated or the higher cost of MMF is an issue. CNI can be used in class V LN at the lowest effective dose, since chronic use of these agents may increase the risk of kidney side effects.

Most renal flares occur within the first 5–6 years following treatment initiation.[24 59–62] Therefore, for most patients it is recommended not to discontinue immunosuppression prior to that time. Therapy deescalation should be contemplated in patients who have attained sustained *complete renal response* and glucocorticoids (GC) should be tapered first. Gradual immunosuppressive drug tapering is recommended prior to complete withdrawal. Both longer duration of treatment and longer duration of remission were associated with reduced risks of kidney flares in patients who discontinued immunosuppressive therapy after 6 years of treatment.[53 63] To this end,

duration of immunosuppressive therapy should be individualised according to the timing and magnitude of response, duration of flare-free maintenance, extra-renal SLE activity and patient preferences.[64]

Non-responding/refractory disease

Failure to achieve the treatment goals described above raises the possibility for non-responding or refractory disease. In this context, proteinuria kinetics are important as a decreasing proteinuria—to a level not yet meeting these targets—could justify further waiting prior to therapy switch, especially in patients with nephrotic-range proteinuria at baseline, provided that kidney function is stable. Thorough assessment, including adherence to treatment with measurement of drug levels, where available, is warranted prior to declaring non-responding/refractory disease (the role of repeat kidney biopsy is discussed below).

All first-line therapies, including MMF/MPA (2–3 g/day),[65] CY and CNI (especially TAC) as monotherapy or 'multitarget' therapy,[66–69] are recommended in non-responding disease. B-cell depleting therapies such as RTX, although off-label, are also indicated either as monotherapy or as add-on therapy to MMF/MPA or CY[70–74]; complete depletion of circulating B-cells predicted clinical remission at 76 weeks.[75] This has recently been supported by a successful trial of obinutuzumab.[76] Following a response to RTX, relapses are not uncommon, but occur after a variable length of time.[77 78] Repeat dose can be considered to prevent or treat a relapse. Although belimumab is not formally indicated for treating LN, post hoc analyses from RCTs and observational studies suggest that, when added to standard-of-care (including MMF), it may gradually reduce proteinuria and the risk for kidney flares.[79–83] Importantly, positive results from the phase III RCT of belimumab as an add-on therapy in LN have been released,[84] and the results of this study are awaited. The combination of RTX and belimumab has recently been used in refractory disease.[85] High-dose intravenous immunoglobulin (2 g/kg) could be considered when there are contraindications to increasing glucocorticoids or immunosuppressive drugs, such as infection,[86] while plasma exchange is rarely indicated.

Adjunct treatment in patients with LN

Renin–angiotensin–aldosterone system blockade is recommended (in non-pregnant patients) due to its antiproteinuric and antihypertensive effects; judicious use and dose titration is warranted in cases of impaired renal function. Hypertension should be controlled to values below 130/80 mm Hg.[87] General kidney-protective measures (eg, avoidance of nonsteroidal anti-inflammatory drugs) cannot be over-emphasised. Vaccination status should be reviewed and patients be vaccinated accordingly with non-live vaccines.[88] Vaccination against influenza and *Streptococcus pneumoniae* are strongly recommended; regarding vaccination against herpes zoster, existing data suggest an acceptable safety profile of the live attenuated vaccine (available in most countries) in patients with lupus. The decision should be individualised, taking into account patient age and net state of immunosuppression. Patients under less intensive immunosuppression may be more appropriate for vaccination.

Statin therapy should be considered on the basis of lipid levels and presence of other cardiovascular risk factors; calculation of the 10-year cardiovascular disease risk using the Systematic Coronary Risk Evaluation, QRisk3, or other validated score is recommended to aid this decision, taking into account that such scores may underestimate the actual risk especially in young patients with SLE .[32 89] Primary prevention of thrombosis with low-dose aspirin is recommended in the presence of high-risk aPL profile, balancing thrombotic versus bleeding risk.[90] Bone protection and prevention of osteoporosis should follow non-pharmacological (exercise uptake, maintenance of normal body mass index) as well as pharmacological measures, according to fracture risk.

Monitoring and prognosis of LN

Patients should be assessed periodically in centres with experienced clinicians interpreting urine microscopy, serology and histology.[91] Kinetics of proteinuria and serum creatinine within the first 6–12 months are more sensitive than haematuria in prred after balancing tedicting long-term prognosis. Quantification of proteinuria can be done by means of a spot UPCR, as its correlation with a 24-hour urine protein collection is high in most studies (although lower when urine protein is <1000 mg/24 hours).[92–94] The 24-hour urine protein may be preferred prior to therapeutic decisions. Urinalysis should be included at each visit; reappearance of glomerular haematuria or cellular casts can be a predictor of impending kidney flare.[95] Serum C3/C4 and anti-dsDNA should be monitored; although a rise in anti-dsDNA titres has been associated with a forthcoming flare, the specificity is modest.[96–98] Anti-C1q antibodies have the highest correlation with active LN and may also predict relapse.[99 100]

Repeat kidney biopsy can be considered in cases of non-responsiveness to immunosuppressive treatment, to differentiate between ongoing activity and irreversible damage, or in cases of relapse. Following a LN flare, histological transition is found in 40%–76%, typically from class V to III–IV forms.[95 101] *Per protocol* repeat biopsies following immunosuppressive treatment frequently show a discordance between clinical and histological response, as 30% of complete responders have ongoing histological activity.[102] The value of protocol rebiopsy to determine the need for continuous treatment was examined in a prospective study of 36 patients with LN who were in complete remission for 12 months, following 3 years of immunosuppressive therapy. Ongoing histological activity was strongly predictive of a subsequent kidney flare when reducing immunosuppression.[103]

Management of ESKD in LN

Recent studies suggest that the risk for ESKD in LN has decreased to <10% in 15 years.[8 12] Still, some patients will progress to irreversible kidney injury, which carries increased risks of morbidity and mortality.[104–106] Once on kidney replacement therapy, the disease usually follows a quiescent course and flares (renal and extra-renal) are less frequent but still can occur. Among kidney replacement modalities, haemodialysis and continuous peritoneal dialysis are accompanied by similar patient survival rates in comparative retrospective studies.[107 108] By contrast, kidney transplantation is associated with higher 10-year patient survival rates[109 110]; data from the United States Renal Data System showed 70% reduced mortality among patients with LN–ESKD who underwent transplantation as compared with non-transplanted counterparts.[111] The updated statement now emphasises that '*transplantation may be preferred over other kidney replacement options and should be considered when extra-renal lupus is clinically (and ideally, serologically) inactive for at least 6 months*'. Currently, only a small fraction of patients undergo pre-emptive transplantation, although this strategy has the most favourable outcome (10-year patient

survival rates 94%,vs 76% and 42%, for peritoneal dialysis and haemodialysis, respectively).[105 112] Transplantation should not be delayed and can be safely performed in the presence of isolated serological activity. Recurrent LN in the transplanted kidney is rarely clinically significant. Patients with transplanted LN are at increased risk of opportunistic infections due to their previous drug exposures.

Antiphospholipid syndrome and LN

Antiphospholipid syndrome-associated nephropathy represents a rare yet distinct type of aPL-induced vascular nephropathy. Although considered a hallmark of antiphospholipid syndrome-associated nephropathy, TMA is not pathognomonic, because similar lesions are found in thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, malignant hypertension or complement-mediated TMA.[113 114] There are no controlled studies to guide the treatment of antiphospholipid syndrome-associated nephropathy. Antiplatelet agents or anticoagulants (if criteria for antiphospholipid syndrome are fulfilled) are recommended, in addition to HCQ. Renin–angiotensin–aldosterone system blockade may delay disease progression.[115]

LN and pregnancy

The 2017 EULAR recommendations for the management of family planning in SLE and antiphospholipid syndrome fully cover the issue of pregnancy, including assisted reproduction, in the context of LN.[116] In the absence of new evidence, the statements of the 2012 recommendations for pregnancy LN were kept unchanged. UPCR should be controlled (ideally, to <500 mg/g) without the use of renin–angiotensin–aldosterone system inhibitors, which are contraindicated in the first trimester due to teratogenicity. Compatible drugs include glucocorticoids, AZA and CNI, and HCQ, which should be continued at safe dosages throughout pregnancy and lactation.[117 118] Withdrawal of MMF for longer period, for example, 6 months before attempts for conception, offers time to assess the tolerability and efficacy of an alternative immunosuppressive.[119] Severe flares during pregnancy—not responding to drugs with an acceptable safety profile—merit multidisciplinary specialist referral; occasionally, termination of pregnancy and/or use of embryotoxic drugs may be considered after balancing the risk/benefit ratio.

Management of paediatric LN

Kidney involvement is more common in childhood compared with adult-onset SLE, often as a presenting manifestation, while renal flares are observed in more than 50% of patients.[120 121] Since the 2012 EULAR/ERA—EDTA recommendations, American and European groups of experts in paediatric SLE and LN have published recommendations for the management of childhood-onset LN; both are largely based on data extrapolation from the studies in adults.[122 123] Notwithstanding differences between children and adults, the respective statements from the 2012 recommendations remained unchanged; diagnosis, treatment (paediatric doses of drugs, online supplementary table 3) and monitoring should follow the same principles as in adult disease. For children in adolescence, a transition programme is recommended to ensure adherence and optimal outcomes.

Additional points to consider and the research agenda in LN are shown in box 1.

Box 1 Research agenda in lupus nephritis

Diagnosis
- Clinical presentation, histopathological features, response to treatments, prognostic factors and genetic background (eg, *APOL1*) in various ethnicities.
- Revision of the International Society of Nephrology/Renal Pathology Society classification criteria (under way).
- Atypical lupus nephritis: podocytopathies and pauci-immune lupus nephritis, other forms.
- Approach to non-lupus (or antinuclear antibody negative) full-house glomerulonephritis.
- Validated definition of kidney flares.

Existing therapies and disease monitoring
- Calcineurin inhibitor efficacy in non-Asian patients.
- B-cell targeting therapies (eg, belimumab, combination of rituximab and belimumab, obinutuzumab) and cytokine inhibitors in lupus nephritis.
- Imaging for kidney fibrosis.
- Duration and withdrawal of therapy.
- Damage accrual in long-term disease.
- Protocolised repeat biopsies: value of early (vs late) repeat biopsy.
- Non-immune mechanisms in progression of lupus nephritis, such as hypertension, obesity, dyslipidaemia.
- Impact of patient education programs.
- Role of eculizumab in antiphospholipid syndrome-associated nephropathy.

Pathophysiology and biomarkers
- Risk stratification of subgroups based on molecular signatures or other biomarkers.
- Explore non-invasive means to classify the types of lupus nephritis and activity status (urine cells, omics, etc).
- Renal progenitor cells and their proliferation in lupus nephritis.
- Kidney repair in lupus nephritis.
- Biomarkers for liquid biopsy.

Lupus nephritis trial design
- Risk stratification of subgroups based on molecular signatures or biomarkers.
- Innovative trial designs.
- Optimisation of 'standard-of-care' (background) treatments.
- Better definition of clinical trial endpoints.

DISCUSSION

Recent insights in LN necessitated an update of the EULAR-ERA/EDTA recommendations, which were developed by a large group of physicians from different specialties and nurses caring for LN, with input from patients, and complement the recently updated recommendations for SLE.[32] Inclusion of all involved medical disciplines is an advantage and accords to the multidisciplinary care that these patients need. These recommendations intend to inform rheumatologists, nephrologists, patients, national professional societies, hospital officials, social security agencies and regulators about the treatment of LN based on most recent evidence, to ensure optimal outcomes with existing therapies. In addition to the quality of evidence for risks and benefits, considerations were also given to the availability and costs of treatments.

A challenging issue is the absence of licenced medications for LN, in spite of high-quality evidence supporting the use of existing drugs. Again, in these recommendations, MMF and low-dose intravenous CY are recommended as drugs of first choice based on their better toxicity profile, while allowing room for the use of high-dose intravenous CY for selected patients with aggressive disease, especially if gonadal toxicity is not a consideration. CNI, especially TAC, in combination with glucocorticoids and MMF in the so called '*multitarget*' therapy, have been included. The absence of robust evidence on CNI in non-Asian populations and their potential for renal toxicity with chronic use has led the committee to adopt a more cautious attitude, recommending them for patients with nephrotic-range proteinuria or not responding to initial therapy. Glucocorticoid usage, in view of their contribution to damage in SLE, received special attention in these recommendations with the committee recommending the use of pulse glucocorticoids, followed by lower doses of daily glucocorticoids to decrease cumulative dose. Glucocorticoid reduction is receiving increased attention in recent years, being used as an outcome measure in SLE trials.[124]

The development of new classification criteria for SLE with increased weighting for kidney disease will facilitate the inclusion of more patients in LN trials.[125] New drugs in development for LN, including novel CNI, B-cell inhibiting and depleting agents, kinase inhibitors, inhibitors of costimulation, inhibitors of complement activation, in combination with improved trial designs, may provide additional agents in the near future.

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Acknowledgements The committee wishes to acknowledge the support of the EULAR Standing Committee on Clinical Affairs. The committee also expresses its sincere appreciation and gratitude to the EULAR Secretariat and especially to Patrizia Jud, executive assistant, for the outstanding organisation.

Contributors AF, MK and KC performed the systematic literature review and AF drafted the manuscript. GB supervised the methodology and edited the manuscript. DJ and DTB convened and supervised the project and edited the manuscript. All authors edited the manuscript and accepted its final form.

Funding This study was funded by European League against Rheumatism.

Competing interests AF reports personal fees from GSK, Abbvie, Amgen, Enorasis, Roche and Genesis Pharma, outside the submitted work. HJA reports personal fees from GSK, Astra Zeneca and Janssen, during the conduct of the study; personal fees from Secarna, Inositec, Previpharma and Noxxon, outside the submitted work. MA reports honoraria fees from GSK and Roche, outside the submitted work; FH reports honoraria fees from GSL, outside the submitted work. MP reports personal fees from Otsuka, grants and personal fees from Alexion, personal fees from Retrophin, outside the submitted work. YKOT reports grants from GSK, personal fees from Aurinia Pharmaceuticals, personal fees from Novartis, during the conduct of the study. MT reports grants from Abbvie, BMS, Novartis, Pfize and Roche and honoraria fees from Novartis, outside the submitted work. DJ reports personal fees from Astra-Zeneca, Aurinia, Boehringer-Ingelheim, grants and personal fees from Chemocentryx, GSK, Roche/Genentech, and Sanofi-Genzyme, personal fees and other from Vifor, outside the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Detailed data relating to this article will be published separately and are also available upon request.

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