Original research

Management of lupus nephritis: a systematic literature review informing the 2019 update of the joint EULAR and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations

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ABSTRACT

Objectives To analyse the current evidence for the management of lupus nephritis (LN) informing the 2019 update of the EULAR/European Renal Association-European Dialysis and Transplant Association recommendations.

Methods According to the EULAR standardised operating procedures, a PubMed systematic literature review was performed, from January 1, 2012 to December 31, 2018. Since this was an update of the 2012 recommendations, the final level of evidence (LoE) and grading of recommendations considered the total body of evidence, including literature prior to 2012.

Results We identified 387 relevant articles. High-quality randomised evidence supports the use of immunosuppressive treatment for class III and class IV LN (LoE 1a), and moderate-level evidence supports the use of immunosuppressive treatment for pure class V LN with nephrotic-range proteinuria (LoE 2b). Treatment should aim for at least 25% reduction in proteinuria at 3 months, 50% at 6 months and complete renal response (<500–700 mg/day) at 12 months (LoE 2a-2b). High-quality evidence supports the use of mycophenolate mofetil/ mycophenolic acid (MMF/MPA) or low-dose intravenous cyclophosphamide (CY) as initial treatment of active class III/IV LN (LoE 1a). Combination of tacrolimus with MMF/MPA and high-dose CY are alternatives in specific circumstances (LoE 1a). There is low-quality level evidence to guide optimal duration of immunosuppression in LN (LoE 3). In end-stage kidney disease, all methods of kidney replacement treatment can be used, with transplantation having the most favourable outcomes (LoE 2b).

Conclusions There is high-quality evidence to guide the initial and subsequent phases of class III/IV LN treatment, but low-to-moderate quality evidence to guide treatment of class V LN, monitoring and optimal duration of immunosuppression.

INTRODUCTION

Lupus nephritis (LN) affects a significant proportion of patients with systemic lupus erythematosus (SLE) and is accompanied by

Key messages

What is already known about this subject?

► Recently, the updated EULAR/ERA-EDTA recommendations for the management of lupus nephritis were published, following a systematic literature review of 15 research questions. The present study outlines the methodology and results of this systematic review.

What does this study add?

► A response in proteinuria within 12 months is the most valuable parameter to predict a favourable long-term outcome in lupus nephritis. Treatment should aim for at least 25% reduction in proteinuria at 3 months, 50% at 6 months and complete renal response (<500–700 mg/day) at 12 months.

► High-quality evidence supports the use of mycophenolate mofetil/mycophenolic acid or low-dose intravenous cyclophosphamide as initial treatment of active class III/IV lupus nephritis.

► Despite the paucity of randomised controlled trials, the recommendation for a lower cumulative glucocorticoid dose adapts to the current trend in SLE therapeutics, towards rationalisation of glucocorticoid use.

How might this impact on clinical practice?

► The updated recommendations will help guide physicians caring for patients with lupus nephritis and the results of this systematic review will serve as evidence base for further future updates.

significant morbidity.[1] To facilitate physician decisions and homogenise patient care, the first set of joint EULAR/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommendations for the management of LN was published in 2012.[2] Since then, a number of randomised

controlled trials (RCTs) have been conducted and meta-analyses of different treatments have been published, while a number of issues regarding optimal monitoring of LN, duration of immunosuppressive treatment and management of end-stage kidney disease (ESKD) are still a matter of debate. To this end, an update of the 2012 recommendations was recently published,[3] with the participation of a multidisciplinary Task Force.

Here, we report the results of the systematic literature review (SLR) which informed the 2019 update of the EULAR/ERA-EDTA recommendations for the management of LN. These were presented to the Task Force during a dedicated meeting, to provide the current evidence base and facilitate the formulation of overarching principles and individual recommendations.

METHODS

We followed the standardised operating procedures for the development of EULAR-endorsed recommendations and employed the Appraisal of Guidelines Research and Evaluation instrument.[4] A Delphi-based methodology within the Task Force identified 15 research questions covering the following topics related to LN: diagnosis and classification, pharmacologic treatment, monitoring and therapeutic targets, refractory LN, management of LN in pregnancy, antiphospholipid syndrome-associated nephropathy, chronic kidney disease, comorbidities and adjunctive therapy. Since this was an update of the 2012 recommendations, the SLR considered all PubMed English-language articles published between January 1, 2012 and December 31, 2018. As the search strategy intended to address 15 different questions, instead of performing a single, broad SLR, we chose to perform focused SLRs for each topic separately. This resulted in 14 dedicated search strings (citations both for induction and for maintenance treatments were retrieved using the same search string). All study designs were included (excluding narrative reviews, viewpoints, opinion or consensus papers), with a minimum of 10 patients/study (except in selected research questions with very limited data). The eligible studies were reviewed for snowball references, and for each eligible study, data extraction concerned parameters for all 15 research questions. A detailed description of the search terms and strategy is provided in online supplementary table 1, and the number of initial articles retrieved and final articles included per research question is shown in table 1.

The SLR was performed by three individuals (questions 1, 2, 7, 9: KC, questions 3, 6, 8, 10–15: AF, questions 4, 5: MK), who independently screened all titles and abstracts to identify studies that were eligible for full-text evaluation. References from included studies were hand-searched to consider any additional relevant articles. An independent data extraction from included papers was performed and evidence was summarised in dedicated tables, which were formulated according to the research question. The level of evidence (LoE) and strength of the recommendations were graded according to the 2009 Oxford Centre for Evidence-Based Medicine,[5] based on the design and validity of available studies. Risk of bias (RoB)[6] was assessed using the Cochrane Risk of Bias Assessment Tool for RCTs and the Newcastle-Ottawa scale for observational studies.[7] The methodologist (GB) reviewed a random 20% of the identified papers to resolve any disagreements in grading of evidence. During the formulation and grading of recommendations (GoR), the final LoE/GoR considered the total body of evidence, including studies published before 2012, as both the convenors (DJ, DTB), the methodologist (GB) and several of the Task Force members had also participated in the 2012 recommendations. An overall detailed description of the results of the SLR is shown in online supplementary table 2.

RESULTS

Predictive value of baseline clinical and histologic parameters for long-term outcomes in lupus nephritis

The SLR identified that, at the time of LN diagnosis, (i) compromised kidney function,[21–28] (ii) hypertension[27 29] and (iii) increased patient age[30–32] have been associated with adverse long-term kidney outcomes. With regard to histologic features, proliferative forms of LN (histologic classes III and IV according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification), increasing percentage of crescents and higher National Institutes of Health histologic activity and chronicity scores have all been associated with adverse long-term kidney outcomes. These associations were confirmed in observational studies captured in the current SLR.[31 33–39] However, from the latter, it became evident that additional histologic features may also carry prognostic implications. Specifically, tubulointerstitial lesions, especially interstitial fibrosis, tubular atrophy or their combination, have been associated with increased risk of ESKD or a composite outcome, in retrospective observational studies.[38 40–42] In a retrospective study of 105 patients with initial renal biopsy between 1987 and 2011 and a 10-year follow-up, presence of interstitial fibrosis/tubular atrophy in >25% of biopsy area was associated with an almost fourfold increased risk for ESKD (HR: 3.89, 95% CI 1.25 to 12.14).[43] Additionally, evidence of thrombotic microangiopathy may be present in 5–25% of patients with LN. Nevertheless, data from observational studies regarding its impact on prognosis are equivocal; six studies have shown association of thrombotic microangiopathy with poor long-term renal outcomes (OR ranging from 2.14 to 5.80) or worse response to treatment,[44–49] while five studies have failed to show such an association.[50–54]

Hydroxychloroquine in lupus nephritis

A detailed SLR concerning the efficacy and safety of hydroxychloroquine (HCQ) was performed in the context of the recently updated EULAR recommendations for the management of SLE.[55] Consequently, the current SLR focused on publications exploring the associations of

Table 1 Numbers of initial articles retrieved and final articles included per research question in the systematic literature review

Question	Initial number of PubMed hits	Final number of studies included
Diagnosis and classification of lupus nephritis		
1. What is the prognostic significance of kidney biopsy findings?	654	33
2. Risk stratification of patients with lupus nephritis by incorporating demographic, clinical and histological data	973	64
Pharmacologic treatment of lupus nephritis		
3. What is the evidence for the benefits and harms of hydroxychloroquine in lupus nephritis?	208	16
4. 'Induction' therapies in lupus nephritis (including dosage of glucocorticoids and use of calcineurin inhibitors)		
5. 'Maintenance' therapies in lupus nephritis (including dosage of glucocorticoids and use of calcineurin inhibitors)	1227	127
Monitoring and therapeutic targets		
6. How should lupus nephritis be monitored?	2739	85
7. What is the goal of treatment in lupus nephritis?	354	18
8. Duration of immunosuppressive treatment in lupus nephritis	98	16
Refractory lupus nephritis		
9. What is the definition of refractory lupus nephritis?	270	13
10. How should refractory/flaring lupus nephritis be treated?	286	36
Special topics in lupus nephritis		
11. Management of lupus nephritis during pregnancy and lactation	173	17
12. Management of antiphospholipid syndrome – nephropathy	345	18
Chronic kidney disease in lupus nephritis		
13. Management of end-stage kidney disease in lupus nephritis	109	42
14. Renal transplantation in patients with lupus nephritis	309	44
Comorbidities and adjunct therapy in lupus nephritis		
15. Comorbidities in lupus nephritis (cardiovascular, infections)	419	49

HCQ specifically with LN outcomes; few such data are available. In individual studies, use of HCQ has been associated with a lower risk for tubulointerstitial inflammation on kidney biopsy[56] and with a higher likelihood for complete response at 1 year.[57] Regarding long-term outcomes, HCQ use has been associated with reduced risk for ESKD/chronic kidney disease (CKD) or doubling of serum creatinine (adjusted HR 0.18–0.40);[27 58 59] a posthoc analysis of the Aspreva Lupus Management Study (ALMS) RCT showed that lack of treatment with antimalarials had more than double risk for treatment failure (defined as death or ESKD or sustained doubling of serum creatinine or renal flare or requirement for rescue therapy) during the maintenance phase (OR 2.4, p = 0.02).[60] Data regarding protection from kidney flares are equivocal[61 62]; a single study showed lower blood concentrations of HCQ in patients with LN who experienced a flare (0.59 vs 0.81 mg/L; p = 0.005).[63]

Initial ('induction') therapies for lupus nephritis and efficacy of calcineurin inhibitors in LN

The SLR identified 13 RCT comparing different regimens for the initial treatment of LN (table 2 and assessment of RoB of individual studies in online supple mentary table 3).

With the exception of the LUNAR trial of rituximab (RTX) in LN, and a recent multicenter phase II RCT testing two doses of the calcineurin inhibitor (CNI) voclosporin, which were both of low RoB, the remaining studies had a higher RoB mainly due to deviations from the intended interventions (blinding) or concerns over the randomisation process (allocation sequence generation and concealment) (table 2). Importantly, five studies compared the two main agents for LN, mycophenolate mofetil (MMF) and cyclophosphamide (CY) (high-dose regimen in three, low dose in one and both regimens in one study), and none found superiority of one regimen over the other. In the LUNAR trial, 144 racially diverse patients with class III–IV LN were randomised to RTX or placebo, together with glucocorticoids and MMF. The study's primary endpoint (complete remission at 52 weeks) was not met, as 26.4% in the RTX versus 30.6% in the placebo group achieved a complete remission at 52 weeks.[15] Seven observational studies (two in pediatric LN) reported on long-term (>3 years) outcomes of patients treated with either CY or MMF as initial

Table 2 Randomised trials of initial ('induction') therapy in lupus nephritis

Reference	n	Ethnicity	Intervention	Comparator	MP pulses and prednisone dosing	HCQ	Endpoint	Results (intervention first)	Risk of bias*
MMF vs CY									
Mendonca et al[8]	40 (1:1)	Indian	MMF 1500 mg bid + P	CY 500–1000 mg/m² monthly + P	MP: 500 mg for 3d P: 0.5 mg/kg/d	NR	CR, PR (24 w)	CR: 52.9% vs 47.8%, p = 0.86 PR: 35.3% vs 39.1%, p = ns	High
Sun et al[9]	82 (1:1)	Chinese	MMF 1000 mg/d + CY 400 mg/m² monthly + P	CY 750 mg/m² monthly + P	MP: no P: 1.0 mg/kg/d for 4–8 w and tapering	NR	RR (24 w)	RR: 88.1% vs 77.5%, p = 0.2	High
Rathi et al[10]	100 (1:1)	Indian	MMF 750–1500 mg bid + P	CY 6×500 mg fortnightly + P	MP: 750 mg for 3d P: 1 mg/kg/d for 8 w and tapering	All patients (6 mg/kg/d)	TRR (24 w)	TR: 76.3% vs 75.0%, p = 0.91	Some concerns
Sedhain et al[11]	42(1:1)	Nepalese	MMF 750 mg bid + P	CY 500–1000 mg/m² monthly + P	MP: no P: 1 mg/kg/d for 4 w tapered to 5–7.5 mg/d	All patients	RR (24 w)	TR: 28.6% vs 19%, p = 0.57	Some concerns
Li et al[12]	60 (1:1:1:1)	Chinese	TAC 0.08–0.1 mg/kg/d (trough blood level of 6–8 ng/mL) + P	MMF 750–1000 mg bid + P vs CY 500–750 mg/m² monthly+P	MP: no P: 0.8–1.0 mg/kg/d for 2 w tapered to 10 mg	NR	CR, PR (24 w)	CR: 45% vs 45% vs 30%, p = 0.65 PR: 30% in each group, p = ns	High
Sahay et al[13]	144 (1:1:1)	Indian	MMF 1200 mg/m²+ P	CY 500 mg/m² monthly (NIH) vs CY 6×500 mg fortnightly (ELNT)	MP: 500 mg/m² for 3d P: 1 mg/kg/d tapered to 10 mg/d	All patients (6 mg/kg/d)	RR (24 w)	RR: 72.9% vs 71.4% (NIH) vs 65% (EuroLupus), p = 0.9	High
Low-dose vs high-dose CY									
Mehra et al[14]	75 (1:1)	Indian	CY 6×500 mg fortnightly + P	CY 6×750 mg/m² four-weekly	MP: 1000 mg for 3 d P: 1 mg/kg/d for 4 w tapered to 5–7.5 mg/d	All patients (5–6 mg/kg/d)	CR, PR (52 w)	CR: 44% vs 65%, p = 0.08 CR/PR: 50% vs 73%, p = 0.04	Some concerns
RTX +MMF vs MMF									
Rovin et al[15]	144 (1:1)	Mixed (White: 31% Black: 28% Hispanic: 36%)	RTX 1000 mg on d 1, 15, 168 and 182+ MMF 3000 mg + P	MMF 3000 mg + P	MP: 1000 mg on d1 and again on 3d P: 0.75 mg/kg/d for 16d and tapered to ≤10 mg/d	44% of patients	CR, PR (52 w)	CR: 26.4% vs 30.6%, p = ns PR: 30.6% vs 15.3%, p = ns	Low
CNI vs SoC									

Continued

Table 2 Continued

Reference	n	Ethnicity	Intervention	Comparator	MP pulses and prednisone dosing	HCQ	Endpoint	Results (intervention first)	Risk of bias*
Mok et al[16]	150 (1:1)	Chinese	TAC 0.06–0.1 mg/kg/d + P	MMF 1000–1500 mg/d bid + P	MP: no P: 0.6 mg/kg/d for 6 w and tapered	51% of patients	CR (24 w)	CR: 62% vs 59%, p = 0.71	Some concerns
Yap et al[17]	16 (1:1) Class V	Chinese	TAC 0.1–0.15 mg/kg/d (trough blood level of 6–8 mg/L) + P	MMF 750–1000 mg bid + P	MP: no P: 0.8 mg/kg/d for 2 w and tapered to 10 mg	NR	CR, PR (106 w)	CR: 11.1% vs 57.1%, p = 0.049 PR: 44.4% vs 14.3%, p = 0.19	High
Li et al[12]	60 (1:1:1)	Chinese	TAC 0.08–0.1 mg/kg/d (trough blood level of 6–8 ng/mL) + P	MMF 750–1000 mg bid + P vs CY 500–750 mg/m² monthly+P	MP: no P: 0.8–1.0 mg/kg/d for 2 w tapered to 10 mg/d	NR	CR, PR (24 w)	CR: 45% vs 45% vs 30% p = 0.65 PR: 30% in each group p = ns	High
Kamanamool et al[18]	83 (1:1)	Thai	TAC 0.1 mg/kg/d (trough level of 6–10 ng/mL) + P	MMF 750–1000 mg bid + P	MP: no P: 0.7–1.0 mg/kg/d for 4 w tapered to 5 mg/d	NR	CR (52 w)	CR: 46.3% vs 57.1%, p = 0.32	Some concerns
Multitarget vs SoC									
Liu et al[19]	362 (1:1)	Chinese	MMF 500 mg bid + TAC 2 mg bid + P	CY 750 mg/m² monthly + P	MP: 500 mg/d for 3 d P: 0.6 mg/kg/d for 4 w tapered to 10 mg/d	NR	CR, PR (24 w)	CR: 45.9% vs 25.6%, p < 0.001 CR/PR: 83.5% vs 63.0%, p < 0.001	Some concerns
Rovin et al[20]	265	Mixed (White: 40.7% Asian: 49.7%)	Voclosporin (low: 23.7 mg bid- or high dose: 39.5 mg bid) + MMF 2000 mg/d + P	MMF 2000 mg/d + P	MP: 500 mg on d0 and d1 P: 20–25 mg/d tapered to 2.5 mg/d at 16 w	NR	CR rate (48 w)	CR rate: lowdose multitarget vs MMF OR = 3.21, p < 0.001 High-dose multitarget vs MMF OR = 2.10, p = 0.026	Low

*Overall risk of bias was assessed using the Revised Cochrane risk-of-bias tool (ROB2).
bid, twice a day; CNI, calcineurin inhibitors; CR, complete response; CY, cyclophosphamide; d, days; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MP, methylprednisolone; NIH, National Institutes of Health; NR, not reported; P, prednisone; PR, partial response; RR, renal response; RTX, rituximab; SoC, standard of care; TAC, tacrolimus; TRR, treatment response rate; w, weeks.

treatment. Although there was a marked heterogeneity between studies (different maintenance treatments and duration of follow-up), the majority of studies did not show any difference in adverse renal outcomes.[26 31 66–70] However, in a posthoc analysis of the ALMS trial, initial treatment with CY was associated with a lower likelihood of treatment failure (OR 0.5, p = 0.05).[60]

Regarding the use of CNI in LN, the majority of studies (RCT and observational) have used tacrolimus (TAC), rather than ciclosporin A (online supplementary table 2, sections 4.1.3 and 4.1.4). CNI (either alone or in combination with MMF) were at least as efficacious as standard of care in a number of RCTs; however, the robustness of evidence is limited as many studies were subject to moderate/high RoB (mostly due to deviations from the intended interventions). A multicenter RCT compared the 'multitarget' therapy (TAC 4 mg/day + MMF 1 g/day) against monthly pulses CY (0.5–1 g/m^2) for induction therapy in 362 Chinese patients with new-onset LN. Both regimens were combined with glucocorticoids. At 6 months, complete renal response rates were 45.9% with the MMF/TAC combination versus 25.6% with CY (p < 0.001).[19] Mok *et al* published a RCT in 150 Chinese patients with classes III–IV (81%) or pure class V (19%) LN, who were randomised to either TAC (0.06–0.1 mg/kg/day) or MMF (2–3 g/day), in a background of prednisone (0.6 mg/kg/day). At 6 months, complete renal response was achieved by 59% of patients in the MMF and 62% of patients in the TAC group (p = 0.71).[16] During maintenance with azathioprine (AZA), proteinuric and nephritic flares developed in 24% of patients and 18% of patients in the MMF group, and 35% (p = 0.12) and 27% (p = 0.21) in the TAC group, respectively. Finally, in the aforementioned phase II RCT comparing two doses of voclosporin in combination to MMF versus MMF alone, the rate of complete response at

48 weeks was significantly higher for both voclosporin groups over MMF alone (OR 3.21, p < 0.001 and 2.10, p = 0.02 for low dose and high dose, respectively, low RoB).[20] Phase III data of voclosporin announced positive results following the completion of the SLR, but the full study has not yet been published.[71]

For class V LN, we found only one small RCT (n = 16) that included exclusively patients with class V, in which MMF was better than TAC in terms of complete renal response (high RoB).[17] A network meta-analysis of 206 patients with class V did not find any difference in renal response or reduction of proteinuria between various treatments (including CNI and MMF).[72] Regarding multitarget treatment, a meta-analysis of 8 trials that compared TAC + MMF versus CY showed superior efficacy of the former in class V (response rate (RR): 4.24, p = 0.02).[73]

No controlled studies have compared different glucocorticoid regimens in the initial phase of LN. Table 3 shows the glucocorticoid tapering schemes of major RCT in LN over the period 2012–2018. Regarding non-controlled studies, a retrospective observational study in two different centres showed that, following initial pulse intravenous methylprednisolone, a lower starting dose of glucocorticoids (≤0.5 mg/kg/day) was as efficacious as a higher dose.[74] In the RITUXILUP observational study, a single RTX dose, combined with MMF and methylprednisolone pulses, and no oral glucocorticoids, was accompanied by high rates of complete/partial response (90%, 45/50 patients) after median 37 weeks.[75]

Subsequent ('maintenance') therapies for lupus nephritis

We found three RCTs specifically designed to compare different treatment regimens for the maintenance therapy in LN (table 4 and assessment of RoB of individual studies in online supplementary table 3). Chen *et al*

Table 3 Dosing regimens of glucocorticoids in major LN RCT from 2012 to 2018

Reference	IV-MP	PO prednisone starting dose	Tapering scheme
Rovin, 2019 (voclosporin)[20]	No	20–25 mg/day for 2 weeks	To 2.5 mg/day at week 16
Rathi, 2016 (MMF vs low-dose CY)[10]	3 × 750 mg	1 mg/kg/day for 8 weeks	Not specified
Mok, 2015 (MMF vs TAC)[16]	No	0.6 mg/kg/day for 6 weeks	By 5 mg/day every week to <10 mg/day, then indefinitely
Liu, 2014 (multitarget vs CY)[19]	3 × 500 mg	0.6 mg/kg/day for 4 weeks	By 5 mg/day every 2 weeks to 20 mg/day, then by 2.5 mg/day every 2 weeks to 10 mg/day
Furie 2014 (abatacept)[64]	No	30–60 mg/day	To 10 mg/day by week 12 recommended
Askanase, 2014 (abatacept)[65]	Optional	60 mg/day for 2 weeks	To 10 mg/day by week 10
Rovin, 2012 (RTX)[15]	3 × 1000 mg	0.75 mg/kg/day (max. 60 mg) until day 16	To 10 mg/day by week 16

CY, cyclophosphamide; IV-MP, intravenous methylprednisolone; LN, lupus nephritis; MMF, mycophenolate mofetil; MP, methylprednisolone; PO, per os; RCT, randomised controlled trial; RTX, rituximab; TAC, tacrolimus.

Table 4 Randomised trials of subsequent ('maintenance') therapy in lupus nephritis

Reference	n	Intervention	Comparator	Prednisone dose	Endpoint	Results	Overall risk of bias*
TAC vs AZA							
Chen et al[76]	70 (1:1)	TAC + P	AZA + P	10 mg/d	24 w relapse	Relapse: AZA vs TAC OR 1.06, p = 0.49	Some concerns
TAC vs MMF							
Yap et al[17]	16 (1:1)	TAC + P	MMF + P	5–7.5 mg/d	106 w, proteinuria, Alb, sCr	Similar levels between arms, p = ns	High
MMF vs AZA							
Kaballo et al[77]	81	MMF + P	AZA + P	1 mg/kg for 4 w tapered to 10 mg/d	Death, ESRD	Composite (death/ESRD) survival rate MMF vs AZA: 95.1% vs 91.3%, p = 0.31	Some concerns

*Overall risk of bias was assessed using the Revised Cochrane risk-of-bias tool (ROB2).
AZA, azathioprine; Alb, albumin; d, days; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; P, prednisone; sCr Serum creatinine; TAC, tacrolimus; w, weeks.

randomised 70 patients to either TAC or AZA following induction; relapse rate did not differ at 24 weeks (OR for relapse of AZA vs TAC: 1.06, p = 0.49), with some concerns regarding RoB.[76] In a smaller study, also in an Asian population, Yap et al compared TAC to MMF in 16 patients; primary endpoint was proteinuria, serum albumin and creatinine at 106 weeks and no differences were found between arms (high RoB).[17] Another RCT compared the efficacy of MMF with AZA in 81 patients with proliferative disease who were previously treated with CY.[77] At 36 months, both the event-free survival rate for the composite endpoint of death or ESKD and the relapse-free survival rate were comparable between arms (95.1% with MMF vs 91.3% with AZA, p = 0.31 and 90.2% with MMF vs 85% with AZA, p = 0.45, respectively).

In addition, the 10-year results of the MAINTAIN trial (AZA vs mycophenolic acid (MPA) for maintenance treatment of LN) represent extended data of a previous RCT.[78] Over 10 years, the two groups experienced similar results in terms of renal flares (45% with MPA, 49% with AZA) and ESKD (7.1% with MPA, 2.2% with AZA). AZA/MPA switch occurred in 20% and 14% of AZA and MPA patients, respectively (RoB 'some concerns'). Additionally, the aforementioned Chinese RCT of 'multitarget' therapy for LN[19] also performed a study on subsequent treatment following induction, comparing TAC/MMF combination to AZA.[79] In this study, 206 patients were randomised to either MMF+TAC (n = 116) or AZA (n = 90), following the same randomisation with the original induction study. At 18 months, no difference in relapse rates was found between the two arms (5.5% in the multitarget vs 7.6% in the AZA, adj. HR: 0.82, p = 0.7). Finally, a favourable effect of MMF over AZA on renal relapse rates has been reported in two meta-analyses (including one network meta-analysis), involving mostly Asian and/or African American populations, and including trials published before the initiation date of the current SLR.[80 81]

Monitoring of lupus nephritis and targets of therapy
The SLR focused on the usefulness of common laboratory tests (serological and urinary) to monitor LN, rather than on various investigational biomarkers that have been used in research studies. In this context, proteinuria and serum creatinine were found to be strongly associated with long-term kidney outcomes. Posthoc analyses of RCT and observational studies have shown that reductions in proteinuria within the first 3, 6 or 12 months are associated with favourable long-term outcomes in LN (table 5 and online supplementary table 4).

Posthoc data from the MAINTAIN and Euro-Lupus Nephritis trials (ELNT) showed that proteinuria values 0.7 and 0.8 gr/day, respectively, had the best predictive value for a serum creatinine <1.0 mg/dL at 7 years.[82 83] This was confirmed in the large Lupus Nephritis Trials Network (LNTN) surrogate marker study which found that higher levels of proteinuria at 12 months conferred a greater risk for CKD, severe kidney injury in both proliferative and membranous LN, and for kidney replacement therapy.[85] Similar results were yielded for serum creatinine at 1 year in the same studies. On the contrary, addition of hematuria to proteinuria and/or serum creatinine not only did not improve, but in some instances decreased the sensitivity of risk models to predict adverse long-term outcomes in LN, in data analysis from ELNT, MAINTAIN, ALMS as well as the LNTN surrogate marker study.

Role of repeat kidney biopsy in lupus nephritis
A total of 26 observational studies since 2012 have evaluated repeat kidney biopsy, performed either per protocol or during an LN flare (online supplementary table 2, section 6.4). Regarding histological transition, the majority of patients with class II (75–80%) progress to class III, IV or V; of patients with class V, 33–43% show histological transition, mostly to proliferative forms. On the contrary, 70–80% of patients with proliferative or mixed classes

Table 5 Performance of different proteinuria cut-off values to predict long-term outcomes in individual studies

Reference	Cut-off and timepoint	Sensitivity	Specificity	PPV	NPV	Outcome
Dall'Era, 2015 (ELNT)[82]	0.8 gr at 12 months	81%	78%	88%	67%	sCr ≤1 at 7 years
Tamirou, 2015 (MAINTAIN)[83]	0.7 gr at 12 months	71%	75%	94%	29%	sCr ≤1 at 7 years
Tamirou, 2016 (MAINTAIN)[78]	0.5 gr at 3/6/ 12 months	NR	NR	89/90/ 92%	21/29/ 32%	sCr ≤120% baseline at 10 years
Dall'Era, 2015 (ALMS)[60]	1 gr at 6 months	NR	NR	NR	NR	OR 0.3 for CR during maintenance
Ugolini-Lopes, 2017[84]	0.8 gr at 12 months	90%	78%	67%	94%	sCr ≤1.5 at 7 years
Yang, 2015[21]	1.2 gr (time-adjusted)	92.1%	83.9%	NR	NR	ESKD

ALMS, Aspreva Lupus Management Study; CR, complete response; ELNT, Euro-Lupus Nephritis Trial; ESKD, end-stage kidney disease; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; sCr, serum creatinine.

remain in proliferative classes. On average, repeat biopsy leads to change in immunosuppressive treatment in >50% of patients (intensification in 70–95%, reduction in 5–30%). Notably, there is often discordance between clinical and histological remission; in one study with 25 repeat biopsies, 60% of patients with an activity index of 0 had residual proteinuria >500 mg/day, while 30% of those with complete clinical response had an activity index >5 in the repeat biopsy.[68] In the Lupus Flares and Histological Renal Activity at the End of the Treatment (LuFla) prospective study, 36 patients who had received ≥36 months of immunosuppression and were in complete response for ≥12 months underwent re-biopsy and subsequent therapy discontinuation; of the 11 patients who flared over the next 2 years, 10 had residual histologic activity in the repeat kidney biopsy.[86]

Duration of immunosuppressive treatment in lupus nephritis

No RCTs have compared different durations of immunosuppressive/biologic treatment in LN and observational data are also limited. In a small RCT, 15 patients with LN and at least partial remission were randomised to either continue or discontinue glucocorticoids.[87] Over 36 months, 4/8 on glucocorticoid continuation exhibited flares compared to 1/7 (14%) in glucocorticoid (GC) withdrawal group (HR: 2.68, p > 0.05). In a single retrospective observational study, immunosuppressive therapy was discontinued in 73 patients who had received median 73 months of therapy; 38% experienced flares at median 3 years following treatment discontinuation. Longer duration of treatment (98 vs 31 months) and longer duration of remission (52.8 vs 12 months) before interruption was associated with a lower risk of flare occurrence.[88] Finally, open-label extensions of RCT and observational studies suggest that the majority of kidney flares tend to occur within the first 5–6 years of therapy; after this point, their rate decreases significantly but does not reach zero.[34 62 78 89 90]

Treatment of refractory lupus nephritis

Available randomised and observational studies regarding the efficacy of different treatments in refractory or relapsing LN are shown in table 6 (and assessment of RoB of individual studies in online supplementary table 3).

A randomised trial comparing CY to mycophenolate sodium in 59 Asian patients showed comparable rates of remission at 12 months (68 vs 70.9%), but the study was prematurely terminated due to more serious adverse events in the CY arm.[91] Another RCT compared the combination of RTX with CY to CY alone in 84 Chinese patients for 12 months; rate of combined complete and partial remission was higher in the RTX/CY combination arm (83.3% vs 57.1%, p < 0.05).[96] The efficacy of RTX has also been tested in various prospective and retrospective observational studies. Overall response rate varies between 53% and 94.1%, and relapse rates vary between 24% and 45% (table 6). MMF has been tested in a single retrospective observational study of 85 patients with refractory LN, previously treated with CY. During a follow-up of 5 years, partial and complete remission was achieved in 60% and 27%, respectively, while 5.8% of patients had progressed to ESKD.[102] Finally, in a pooled posthoc analysis of the BLISS trials, belimumab has shown antiproteinuric effect and fewer renal relapses in a mixed new-onset and refractory LN population.[103] More recently, a phase III RCT of belimumab compared to placebo (both combined with standard of care) in LN announced positive results meeting its primary endpoint (renal response in 2 years); however, the results of the trial are yet to be published.[104]

Management of end-stage kidney disease in lupus nephritis

A meta-analysis of 187 articles and a total of 18 309 patients reported that the 5-year risk of ESKD in developed countries decreased from 16% in the period 1970–1979 to 11% in the mid-1990s, showing a plateau thereafter.[105] The risk of ESKD in developing countries was higher. After reaching ESKD, all methods of kidney replacement therapy (haemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (KT)) can be used in patients with LN. A study using data from the United States Renal Data

Table 6 Efficacy of different therapeutic agents in refractory/non-responding or flaring LN

Reference	Type of study	n	Intervention	Control	Endpoint	Results	Risk of bias*
CY							
Anutrakulchai et al[91]	RCT	CY:32 EC-MPS: 27	CY + P	EC-MPS + P	12 m CR, PR, TF	CR+PR: CY vs EC-MPS 68% vs 71%, p = ns TF: CY vs EC-MPS 46.9% vs 37%, p = ns *Premature termination due to high rate of serious adverse events in CY arm*	High
Moroni et al[92]	Observational	CY:14 RTX:10	PO CY + P	RTX + P	3y CR	CR: CY vs RTX 92% vs 80%	7
Multitarget							
Choi et al[93]	Observational	29	MMF + TAC + P	-	12 m CR, PR	CR: 25.9% PR: 29.6%	4
Mok et al[94]	Observational	21	MMF + TAC + P	-	12 m CR, PR	CR+PR: 67%	5
Kasitanon et al[95]	Observational	21	MMF + CsA + P add-on to IS	-	12 m CR, PR	CR: 33.3% PR: 38.1%	5
RTX							
Zhang et al[96]	RCT	84 (1:1)	CY + RTX + P	CY + P	12 m CR, PR	CR+ PR: CY vs RTX+CY 57.1% vs 83.3% p < 0.05	High
Kotagiri et al[97]	Observational	14	RTX + p add-on to IS	-	18 m CR, PR, Relapse	CR+PR: 79% Relapse: 45%	4
Davies et al[98]	Observational	18	RTX + CY + P	-	12 m CR, PR, Relapse	CR+PR: 72% Relapse: 39%	5
Jonsdottir et al[99]	Observational	25	RTX + CY + P	-	36 m CR, PR, Relapse	CR: 64% PR: 88% Relapse: 24%	6
Iaccarino et al[100]	Observational	68	RTX + P± CY	-	12 m CR, PR, Relapse	CR+PR: 94.1% Relapse: 29.4%	6
Contis et al[101]	Observational	17	RTX + P	-	52 w CR, PR	CR+PR: 53%	4
MMF							
Rivera et al[102]	Observational	85	MMF + P	-	60 m CR, PR, Relapse	CR: 27% PR: 60% Relapse: 15.7%	5

*Overall risk of bias was assessed using the Revised Cochrane risk-of-bias tool (ROB2) for RCT and the Newcastle-Ottawa scale for observational studies.

CY, cyclophosphamide; CR, complete response; CsA, ciclosporin A; EC-MPS, enteric-coated mycophenolate sodium; IS, immunosuppressant; m, months; MMF, mycophenolate mofetil; P, prednisone; PR, partial response; RCT, randomised controlled trial; RTX, rituximab; TF, treatment failure; TAC, tacrolimus; w, weeks; y, years.

System (USRDS) on 11 317 LN patients reported that 82.0% initiated HD, 12.2% initiated continuous PD and only 2.8% underwent KT.[106] We identified five retrospective studies that have compared the three modalities, as regards to patient outcomes in LN (online supplementary table 5).[107–111] In three studies, HD was compared to continuous PD, while in two additional studies,[108 111] a KT arm was also included. In the studies comparing HD to PD, no difference was found in overall patient survival; in the two studies that included a KT arm, the latter was found to be associated with higher patient survival rates at 1, 5 and 10 years. Recent data from the USRDS comparing LN-

ESKD patients who underwent transplantation versus those who did not (total 9659 patients) showed a 70% reduction in all-cause mortality (adj. HR: 0.30, 95% CI 0.27 to 0.33), along with reductions in cause-specific mortality (CVD, infections, sepsis, etc).[112]

Cardiovascular risk and risk for infections in patients with lupus nephritis

Similar to the question on HCQ, a focused SLR regarding infections and cardiovascular disease (CVD) in general SLE was performed in the context of the EULAR recommendations for the management of SLE.[55] The current SLR focused on publications exploring the associations of

these comorbidities specifically with LN. Both disease- and treatment-related factors account for an increased CVD risk in LN. A single meta-analysis correlated LN with CVD (OR 1.6, 95% CI 1.04 to 2.60, although not reporting clearly on the heterogeneity of reported studies)[113]; however, a number of low-quality trials have failed to prove a significant association. Similarly, contradictory results were obtained from studies that used surrogate CVD endpoints, such as subclinical atherosclerosis.[114–117] In the single prospective trial that explored the possible atheroprotective effect of ACE inhibitors and angiotensin receptor blockers in patients with LN, there was no difference in the cumulative occurrence of CVD between the treatment and the control arm (p = 0.7).[118] The increased risk for infections in patients with LN is supported by a number of studies (HR: 1.4—5.3)[119–122]; regarding treatment-related risk factors, a network meta-analysis of 32 RCTs identified that high-dose GC therapy was associated with the highest risk for serious infections compared to TAC as reference drug (OR 12.8, 95% CI 1.53 to 119.90), followed by low-dose CY (OR 4.8, 95% CI 1.48 to 17.64) and high-dose CY (OR 6.6, 95% 2.25 to 20.50).[123]

DISCUSSION

Kidney involvement in SLE has significant implications for the disease management and prognosis. Several authorities, including the Kidney Disease Improving Global Outcomes (KDIGO) and American College of Rheumatology, have published recommendations for the management of LN.[124] The recently published update of the joint EULAR/ERA-EDTA recommendations was based on a dedicated SLR, which covered several aspects of the disease (formed in the 15 research questions) and not just the efficacy and safety of immunosuppressive agents used in the treatment of its different phases. To this end, we followed an inclusive approach during article selection, in order to capture data from observational and non-controlled studies, in topics where randomised controlled studies are absent or scarce. Importantly, because this was an update of previous recommendations published in 2012,[2] data retrieval started from the ending date of the previous SLR, although overall LoE and GoR took into account the whole body of evidence.

Kidney biopsy remains a cornerstone in the diagnosis and management of LN, because the prognostic value of histological findings cannot be replaced by any clinical or laboratory parameter. In addition to features with well-established prognostic value (histological class, activity and chronicity indices, presence of crescents), from the review of the literature it became evident that acute or chronic lesions of the tubulointerstitial space (inflammation and fibrosis/tubular atrophy, respectively) are also associated with adverse short- and long-term outcomes. Regarding features of thrombotic microangiopathy, prognostic associations are more equivocal, despite the fact that such lesions may be present in up to one in four

kidney biopsies in LN. A current revision of the 2003 ISN/RPS class, which will address these issues, is currently under way. The issue of repeat kidney biopsy, performed either per protocol or during a disease flare, was explored in several observational studies; histological transition is common, often leading to changes in treatment.

Regarding management of LN, our SLR confirmed the equal efficacy of MMF and CY for the initial ('induction') phase of LN, as evidenced by a number of RCTs in different ethnic/racial groups, which was recently suggested also by a Cochrane systematic review.[80] Importantly, the low-dose CY regimen (ELNT) was tested also in non-exclusively Caucasian populations, with similar results.[10 13 14 65] Regarding the use of CNI or 'multitarget' therapy (combination of CNI with MMF), it is important to point out that the majority of studies (both randomised and observational) testing this class of drugs have used TAC, hence the respective clarification in the manuscript of the updated EULAR/ERA-EDTA recommendations.[55] The scepticism raised by the fact that initial studies using the multitarget regimen were performed in Asian populations has been partly addressed by the multi-ethnic phase II study of voclosporin/MMF combination[20]; the results of the phase III study, which recently announced positive results, are expected to provide more data regarding a possible future universal recommendation of multitarget regimens for LN.

A GC dosing regimen pointing towards lower cumulative GC doses was suggested in the recommendations, stating that 'the use of IV 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'. Unfortunately, there is a paucity of RCTs that have directly compared different glucocorticoid regimens in LN. Apart from the uncontrolled studies mentioned in the "Results" section, the older open-label, controlled MyLupus study (not included in the current SLR) had shown that lower CG doses with enteric-coated mycophenolate sodium were accompanied by similar rates of complete response at 24 weeks.[125] Importantly, the need to minimise the use of GC in general SLE was also emphasised in the 2019 updated EULAR recommendations for the management in SLE.[55] Ultimately, despite the lack of robust data, the current recommendations attempt to adapt to the current trend in SLE therapeutics, towards a rationalisation of GC use, with concurrent capitalisation of potent immunosuppressive agents.[126]

In terms of monitoring of LN, a number of posthoc analyses of major studies in LN suggested the value of an early proteinuria response, together with a normal serum creatinine, within 12 months, to predict a favourable long-term outcome of patients.[60 82–85] By contrast, glomerular haematuria was consistently shown in the same studies to add no predictive value in these prognostic models. Although these findings may not necessarily impact routine clinical practice, where urine microscopy will continue to be part of patient monitoring, however, they

may well carry implications regarding future design of optimal endpoints for clinical trials. Haematuria may be particularly persistent to immunosuppressive treatment; its omission from the components of a 'clinical response', owing to its poor prognostic value, may allow more clinical trials of drugs under investigation to reach their target.[127] Facing a flare or prior to labelling a patient with LN as 'refractory to treatment', a thorough investigation of possible causes is mandatory. In this regard, assessment of adherence to treatment is of utmost importance; suboptimal compliance rates, especially with HCQ, have been documented in SLE and may correlate with LN flares.[128]

In summary, the SLR that supported the update of the joint EULAR/ERA-EDTA recommendations found a high quality of data regarding induction and maintenance treatments in the management of LN, but low-to-moderate quality concerning most other aspects of this disease. Issues like long-term efficacy and safety of novel treatment regimens, optimal duration of immunosuppressive therapy after patients reach remission or the role of repeat kidney biopsy need to be further explored.

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