Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis

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ABSTRACT

Objectives To develop recommendations for the management of adult and paediatric lupus nephritis (LN).

Methods The available evidence was systematically reviewed using the PubMed database. A modified Delphi method was used to compile questions, elicit expert opinions and reach consensus.

Results Immunosuppressive treatment should be guided by renal biopsy, and aiming for complete renal response (proteinuria <0.5 g/24 h with normal or near-normal renal function). Hydroxychloroquine is recommended for all patients with LN. Because of a more favourable efficacy/toxicity ratio, as initial treatment for patients with class III–IV$_A$ or $_{A/C}$ (±V) LN according to the International Society of Nephrology/Renal Pathology Society 2003 classification, mycophenolic acid (MPA) or low-dose intravenous cyclophosphamide (CY) in combination with glucocorticoids is recommended. In patients with adverse clinical or histological features, CY can be prescribed at higher doses, while azathioprine is an alternative for milder cases. For pure class V LN with nephrotic-range proteinuria, MPA in combination with oral glucocorticoids is recommended as initial treatment. In patients improving after initial treatment, subsequent immunosuppression with MPA or azathioprine is recommended for at least 3 years; in such cases, initial treatment with MPA should be followed by MPA. For MPA or CY failures, switching to the other agent, or to rituximab, is the suggested course of action. In anticipation of pregnancy, patients should be switched to appropriate medications without reducing the intensity of treatment. There is no evidence to suggest that management of LN should differ in children versus adults.

Conclusions Recommendations for the management of LN were developed using an evidence-based approach followed by expert consensus.

INTRODUCTION

Approximately 50% of patients with systemic lupus erythematosus (SLE) will develop lupus nephritis (LN), which increases the risks for renal failure, cardiovascular disease and death. In 2008, we published the first European League Against Rheumatism (EULAR) recommendations on the management of SLE.[1] Since then, several controlled trials have been published upon which updated recommendations can be based. The realisation that in the care of patients with LN internists/rheumatologists and nephrologists are involved, prompted us to develop recommendations for LN under the joint auspices of the EULAR and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA), with experts from both disciplines. The panel was enriched with renal pathologists and paediatricians with expertise on LN.

METHODS

We followed the EULAR standardised operating procedures[2] and the Appraisal of Guidelines Research and Evaluation instrument. We selected a list of questions by a modified Delphi method further edited for literature search, followed by a systematic search of the PubMed database (web-only appendix tables 1 and 2); all English language publications up to December 2011 were considered. We further refined retrieved items based on abstract and/or full-text content, and the number of patients (requiring n≥30 for diagnosis, monitoring, prognosis; n ≥ 10 for treatment). A detailed presentation of the literature review is provided in web-only appendix table 3. Evidence was categorised based on the design and validity of available studies and the strength of the statements was graded. After discussions, the committee arrived at 28 final statements rated individually by each member (tables 1 and 2).

Recommendations

Table 1 Recommendations for the management of patients with systemic lupus erythematosus (SLE) with renal involvement

Statement	Mean (SD)	Median (IQR)*
1. Indications for first renal biopsy in SLE		
Any sign of renal involvement—in particular, urinary findings such as reproducible proteinuria ≥0.5 g/24 h especially with glomerular haematuria and/or cellular casts—should be an indication for renal biopsy. Renal biopsy is indispensable since in most cases, clinical, serological or laboratory tests cannot accurately predict renal biopsy findings.	9.7 (0.5)	10 (1)
2. Pathological assessment of kidney biopsy		
The use of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system is recommended with assessment of active and chronic glomerular and tubulointerstitial changes, and of vascular lesions associated with anti-phospholipid antibodies/syndrome	9.6 (0.7)	10 (1)
3. Indications and goals of immunosuppressive treatment in lupus nephritis (LN)		
3.1. Initiation of immunosuppressive treatment should be guided by a diagnostic renal biopsy. Immunosuppressive agents are recommended in class III$_A$ or III$_{A/C}$ (±V) and IV$_A$ or IV$_{A/C}$ (±V) nephritis, and also in pure class V nephritis if proteinuria exceeds 1 g/24 h despite the optimal use of renin-angiotensin-aldosterone system blockers	9.4 (0.7)	10 (1)
3.2. The ultimate goals of treatment in LN are long-term preservation of renal function, prevention of disease flares, avoidance of treatment-related harms, and improved quality of life and survival. Treatment should aim for complete renal response with UPCR <50 mg/mol and normal or near-normal (within 10% of normal GFR if previously abnormal) renal function. Partial renal response, defined as ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal renal function, should be achieved preferably by 6 months but no later than 12 months following initiation of treatment	9.6 (0.8)	10 (1)
4. Treatment of adult LN		
Initial treatment		
4.1. For patients with class III$_A$ or III$_{A/C}$ (±V) and class IV$_A$ or IV$_{A/C}$ (±V) LN, mycophenolic acid (MPA) (mycophenolate mofetil (MMF) target dose: 3 g/day for 6 months, or MPA sodium at equivalent dose) or low-dose intravenous cyclophosphamide (CY) (total dose 3 g over 3 months) in combination with glucocorticoids, are recommended as initial treatment as they have the best efficacy/toxicity ratio	9.3 (0.8)	9 (1)
4.2. In patients with adverse prognostic factors (acute deterioration in renal function, substantial cellular crescents and/or fibrinoid necrosis), similar regimens may be used but CY can also be prescribed monthly at higher doses (0.75–1 g/m^2) for 6 months or orally (2–2.5 mg/kg/day) for 3 months	8.8 (1.3)	9 (2)
4.3. To increase efficacy and reduce cumulative glucocorticoid doses, treatment regimens should be combined initially with three consecutive pulses of intravenous methylprednisolone 500–750 mg, followed by oral prednisone 0.5 mg/kg/day for 4 weeks, reducing to ≤10 mg/day by 4–6 months	9.0 (1.1)	9 (2)
4.4. In pure class V nephritis with nephrotic-range proteinuria, MPA (MMF target dose 3 g/day for 6 months) in combination with oral prednisone (0.5 mg/kg/day) may be used as initial treatment based on better efficacy/toxicity ratio. CY or calcineurin inhibitors (ciclosporin, tacrolimus) or rituximab are recommended as alternative options or for non-responders.	8.9 (1.2)	9 (2)
4.5. Azathioprine (AZA) (2 mg/kg/day) may be considered as an alternative to MPA or CY in selected patients without adverse prognostic factors (as defined in 4.2), or when these drugs are contraindicated, not tolerated or unavailable. Azathioprine use is associated with a higher flare risk.	8.6 (1.3)	9 (2)
Subsequent treatment		
4.6. In patients improving after initial treatment, subsequent immunosuppression is recommended with either MPA at lower doses (initial target MMF dose 2 g/day) or AZA (2 mg/kg/day) for at least 3 years, in combination with low dose prednisone (5–7.5 mg/day). Gradual drug withdrawal, glucocorticoids first, can then be attempted.	9.4 (0.9)	10 (1)
4.7. Patients who responded to initial treatment with MPA should remain on MPA unless pregnancy is contemplated, in which case they should switch to AZA at least 3 months prior to conception	9.4 (0.8)	10 (1)
4.8. Calcineurin inhibitors can be considered in pure class V nephritis	9.1 (1.2)	10 (2)
Refractory disease		
4.9. For patients who fail treatment with MPA or CY either because of lack of effect (as defined in 3.2) or due to adverse events, we recommend that the treatment is switched from MPA to CY, or CY to MPA, or rituximab be given	9.2 (1.0)	10 (1)
5. Adjunct treatment in patients with LN		
5.1. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers are indicated for patients with proteinuria (UPCR >50 mg/mmol) or hypertension	9.7 (0.8)	10 (0)
5.2. Cholesterol lowering with statins is indicated for persistent dyslipidaemia (target low-density lipoprotein (LDL)-cholesterol 2.58 mmol/litre (100 mg/dl))	9.2 (1.3)	10 (1)
5.3. Hydroxychloroquine is recommended to improve outcomes by reducing renal flares and limiting the accrual of renal and cardiovascular damage	9.3 (1.7)	10 (1)
5.4. Acetyl-salicylic acid in patients with anti-phospholipid antibodies, calcium and vitamin D supplementation, and immunisations with non-live vaccines may reduce treatment or disease-related comorbidities and should be considered	9.3 (1.3)	10 (1)
5.5. Consider anticoagulant treatment in nephrotic syndrome with serum albumin <20 g/litre, especially if persistent or in the presence of anti-phospholipid antibodies	9.2 (1.1)	10 (1)
6. Monitoring and prognosis of LN		
6.1. Active LN should be regularly monitored by determining at each visit body weight, blood pressure, serum creatinine and eGFR, serum albumin, proteinuria, urinary sediment (microscopic evaluation), serum C3 and C4, serum anti-dsDNA antibody levels and complete blood cell count. Anti-phospholipid antibodies and lipid profile should be measured at baseline and monitored intermittently.	9.3 (0.9)	10 (1)
6.2. Changes in serum creatinine (eGFR), proteinuria, haemoglobin levels and blood pressure are predictors of long-term outcome in LN	9.2 (1.2)	10 (1)
6.3. Visits should be scheduled every 2–4 weeks for the first 2–4 months after diagnosis or flare, and then according to the response to treatment. Monitoring for renal and extra-renal disease activity should be lifelong at least every 3–6 months.	9.1 (1.4)	10 (1)
6.4. Repeat renal biopsy may be used in selected cases, such as worsening or refractoriness to immunosuppressive or biological treatment (failure to decrease proteinuria by ≥50%, persistent proteinuria beyond 1 year and/or worsening of GFR), or at relapse, to demonstrate change or progression in histological class, change in biopsy chronicity and activity indices, to provide prognostic information, and detect other pathologies	9.2 (1.4)	10 (1)

Continued

Table 1 Continued

Statement	Mean (SD)	Median (IQR)*
7. Management of end-stage renal disease (ESRD) in LN		
7.1. All methods of renal replacement treatment can be used in patients with lupus, but there may be increased risk of infections in patients on peritoneal dialysis still on immunosuppressive agents and vascular access thrombosis in patients with anti-phospholipid antibodies	9.5 (0.8)	10 (1)
7.2. Transplantation should be performed when lupus activity has been absent, or at a low level, for at least 3– 6 months, with superior results obtained with living donor and pre-emptive transplantation. Anti-phospholipid antibodies should be sought during transplant preparation because they are associated with an increased risk of vascular events in the transplanted kidney.	9.4 (0.9)	10 (1)
8. Anti-phospholipid syndrome-associated nephropathy in SLE		
In patients with lupus and anti-phospholipid syndrome (APS)-associated nephropathy (APSN), hydroxychloroquine and/or antiplatelet/anticoagulant treatment should be considered	9.0 (1.4)	9 (2)
9. LN and pregnancy		
9.1. Pregnancy may be planned in stable patients with inactive lupus and UPCR <50 mg/mmol, for the preceding 6 months, with GFR that should preferably be >50 ml/min. Acceptable medications include hydroxychloroquine, and where needed, low dose prednisone, azathioprine and/or calcineurin inhibitors. The intensity of treatment should not be reduced in anticipation of pregnancy. During pregnancy, acetylsalicylic acid should be considered to reduce the risk of pre-eclampsia. Patients should be assessed at least every 4 weeks, preferably by a specialist physician and obstetrician.	9.3 (1.0)	10 (1)
9.2. Flare of LN during pregnancy can be treated with acceptable medications stated above depending on severity of flare	9.0 (1.5)	10 (2)
10. Management of paediatric LN		
Compared to adult-onset disease, LN in children is more severe with increased damage accrual and more common at presentation but the diagnosis, management and monitoring is similar to that of adults. A coordinated transition programme to adult specialists is important in assessing concordance to treatments and optimising long-term outcomes.	9.6 (0.7)	10 (1)

*Numbers are mean (SD) and median (IQR) agreement level among experts. A score of 10 represents the highest level of agreement.
GFR, glomerular filtration rate; UPCR, urine protein:creatinine ratio.

RESULTS AND DISCUSSION

Indications for first renal biopsy in SLE

Because of the potentially aggressive nature of LN, the thresholds for performing a renal biopsy should be low. Any sign of renal involvement—in particular, reproducible proteinuria ≥0.5 g/24 h especially with glomerular haematuria and/or cellular casts—can be an indication for biopsy. Clinical, serological or laboratory tests cannot accurately predict histological findings. Although clinically relevant biopsy findings are more common in the presence of significant proteinuria, a biopsy may also be considered in cases of persisting isolated glomerular haematuria, isolated leucocyturia (after other causes, such as infection or drugs are excluded),[3] [4] and the rare occurrence of unexplained renal insufficiency with normal urinary findings. Lower glomerular filtration rate (GFR) is associated with chronic histological lesions and faster rate of decline in GFR.[5–9] Methods for estimating GFR such as the Cockcroft–Gault and the Modification of Diet in Renal Disease equations in adults or the Schwartz formula in children, although not fully validated in SLE,[10] [11] are acceptable in clinical practice. For GFR <30 ml/min the decision for biopsy should be based on normal kidney size (>9 cm length in adults) and/or evidence of renal disease activity, in particular proteinuria and active urinary sediment (dysmorphic red blood cells (glomerular haematuria), white blood cells and/or cellular casts). Biopsy should be performed within the first month after disease onset, preferably before the institution of immunosuppressive treatment, unless contraindicated.[12–14] Treatment with high-dose glucocorticoids should not be delayed if a renal biopsy cannot be readily performed.

Pathological assessment of renal biopsy

We recommend using the International Society of Nephrology/Renal Pathology Society 2003 classification system[15–17] with assessment of active and chronic glomerular and tubulointerstitial changes,[18–21] and of vascular lesions associated with anti-phospholipid antibodies/syndrome.[22] [23] An adequate sample of ≥8 glomeruli should be examined under light microscopy[15] [24] with haematoxylin and eosin, periodic acid-Schiff, Masson's trichrome and silver stain. Immunofluorescence or immunohistochemistry for immunoglobulin and complement deposits (IgG, IgA, IgM, C3, C1q, κ and λ light chains) is recommended.[12] [21] [25] [26] Electron microscopy facilitates the recognition of proliferative and membranous lesions and should be performed if possible.[19] [27–29]

Indications and goals of immunosuppressive treatment in LN

Ultimate goals of treatment are long-term preservation of renal function, prevention of flares, avoidance of treatment-related harms, and improved quality of life and survival. Treatment must be based on a shared decision between patient and doctor. Immunosuppressive treatment is generally not indicated in classes I and VI LN, unless necessitated by extra-renal lupus activity.[30–32]

Treatment should aim for complete renal response, defined as urine protein:creatinine ratio (UPCR) <50 mg/mmol (roughly equivalent to proteinuria <0.5 g/24 h) and normal or near-normal (within 10% of normal GFR if previously abnormal) GFR. Partial renal response, defined as ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR, should be achieved preferably by 6 months and no later than 12 months following treatment initiation.[9] [33–35] Improvement includes any reduction in proteinuria and normalisation or stabilisation of GFR. Although partial response carries worse prognosis than complete response,[34] [36] [37] it may be an acceptable outcome when all treatments have been exhausted or cannot be used due to high individual risks for toxicity. Following response, patients may experience nephritic or proteinuric flares, the former having more adverse impact on renal outcomes.[34] [37–39] Nephritic flares include reproducible increase of serum creatinine by ≥30% (or, decrease in GFR by ≥10%) and active urine sediment with increase in glomerular haematuria by ≥10 red blood cells per high power field, irrespective of changes in proteinuria; proteinuric flares include reproducible doubling of UPCR to >100 mg/mmol after complete response or reproducible doubling of UPCR to >200 mg/mmol after partial response.[34] [37] [38]

Recommendations

Table 2 Category of evidence and strength of statements*

Statement/item	Level of evidence	Strength of statement
1. Indications for first renal biopsy		
Diagnostic value of urinary findings (proteinuria ≥0.5 g/24 h especially with glomerular haematuria and/or cellular casts)	2	C
Clinical, serological or laboratory tests correlate modestly with renal biopsy findings	2	B
2. Pathological assessment of kidney biopsy		
International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system preferred	2	C
Prognostic value of glomerular changes	1	A
Prognostic value of activity and chronicity indices	1	A
Prognostic value of tubulointerstitial lesions	2	B
Prognostic value of vascular lesions associated with anti-phospholipid antibodies	3	C
3. Indications for immunosuppressive treatment and treatment strategy		
Diagnostic renal biopsy required	–	C
Immunosuppression for class III$_A$ or III$_{A/C}$ (±V) and IV$_A$ or IV$_{A/C}$ (±V) nephritis	1	A
Immunosuppression for class V nephritis if proteinuria >1 g/24 h	4	C
Target: preservation of renal function, prevention of disease flares, avoidance of treatment-related harms and improved quality of life and survival	–	C
Prognostic value of complete renal response (UPCR <50 mg/mmol and normal or near-normal GFR)	1	B
Prognostic value of partial renal response (≥50% reduction in proteinuria and normal or near-normal GFR)	1	B
4. Treatment of adult lupus nephritis (LN)		
Class III$_A$ or $_{A/C}$ (±V) and class IV$_A$ or $_{A/C}$ (±V): glucocorticoids plus		
Mycophenolic acid (MPA)	1	A†
Low-dose intravenous cyclophosphamide (CY)	1	B
If adverse clinical/histological prognostic factors are present: glucocorticoids plus		
MPA	2	B
Low-dose intravenous CY	4	C
High-dose intravenous CY	1	A
Oral CY	3	B
Use of glucocorticoids		
Three consecutive pulses of intravenous methylprednisolone 500–750 mg	3	C
Then, oral prednisolone 0.5 mg/kg/day for 4 weeks with subsequent tapering	–	C
Pure class V nephritis with nephrotic-range proteinuria: glucocorticoids plus		
MPA	2	B
High-dose intravenous CY	2	A
Ciclosporin (increased rates of relapse of nephrotic syndrome)	2	A
Tacrolimus	3	B
Rituximab	4	C
Azathioprine (AZA) use in LN		
In selected patients without adverse clinical or histological prognostic factors		
Class III–IV nephritis	2	B
Class V nephritis (non-nephrotic-range proteinuria)	4	C
When MPA or CY are contraindicated, not tolerated, or unavailable	–	C
Associated with higher relapse risk	2	B
Subsequent immunosuppression in class III–IV or V nephritis		
MPA or AZA, in combination with low-dose glucocorticoids	1	A
Successful induction with MPA followed by continuing MPA	–	C
AZA preferred if pregnancy planned	–	C
Duration of immunosuppressive treatment: at least 3 years	3	C
Gradual drug withdrawal, glucocorticoids first, can then be attempted	–	C
Calcineurin inhibitors can be considered in pure class V nephritis	4	C
Failure to treatment with MPA or CY		
Switch from MPA to CY	4	C
Switch from CY to MPA	4	C
Add or switch to rituximab	4	C
5. Adjunct treatment		
Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for proteinuria or hypertension	2	B
Cholesterol lowering with statins for persistent dyslipidaemia	–	C
Hydroxychloroquine	3	C
Acetyl-salicylic acid in patients with anti-phospholipid antibodies	–	C
Calcium and vitamin D supplementation	–	C

Continued

Table 2 Continued

Statement/item	Level of evidence	Strength of statement
Immunisations with non-live vaccines	–	C
Anticoagulant treatment in nephrotic syndrome with serum albumin <20 g/litre	–	C
Monitoring and prognosis of LN		
Serum creatinine and GFR, proteinuria, and urinary microscopy to define activity	–	C
Body weight and blood pressure measurement to assess activity and response to treatment	–	C
Diagnostic utility of		
Serum C3	2	B
Serum C4	2	B
Serum anti-dsDNA	2	B
Complete blood cell count	3	C
Serum albumin	3	C
Prognostic value of		
Anti-phospholipid antibodies	2	B
Serum lipids	2	B
Prognostic value of serial changes in		
Serum creatinine/GFR	1	A
Proteinuria	1	A
Haemoglobin	2	B
Blood pressure	1	A
Frequency of monitoring		
Every 2–4 weeks for the first 2–4 months after diagnosis or flare	–	C
Lifelong at least 3–6 monthly	–	C
Repeat renal biopsy		
Useful in worsening or refractory disease or at relapse	3	C
Strong prognostic value of renal biopsy findings	2	B
7. End-stage renal disease (ESRD) in systemic lupus erythematosus (SLE)		
All methods of renal replacement treatment are safe	2	B
Increased risk for infections in patients on peritoneal dialysis	2	B
Increased risk for vascular access thrombosis with anti-phospholipid antibodies	3	C
Transplantation.		
Better outcome when lupus activity is absent or at a low level for 3–6 months	3	C
Better outcome with living versus cadaveric donor	2	B
Better outcome with pre-emptive transplantation	3	C
Increased risk for vascular events in patients with anti-phospholipid antibodies	2	B
8. Treatment of anti-phospholipid syndrome (APS)-associated nephropathy (APSN)		
Hydroxychloroquine	–	C
Antiplatelet/anticoagulation treatment	–	C
9. LN and pregnancy		
Safe in inactive SLE with UPCR <50 mg/mmol for the preceding 6 months	2	B
GFR preferably above 50 ml/min	–	C
Safety and efficacy of the following medications		
Hydroxychloroquine	3	B
Low-dose prednisone	4	C
Azathioprine	4	C
Calcineurin inhibitors	4	C
Intensity of treatment should not be reduced in anticipation of pregnancy	–	C
Acetylsalicylic acid to reduce the risk of pre-eclampsia	3	C
Assessment every 4 weeks, preferably by a specialist physician and obstetrician	–	C
Flare of nephritis can be treated with same acceptable medications but also with calcineurin inhibitors, intravenous immunoglobulin, immunoadsorption and plasma exchange	–	C
10. Paediatric LN		
More common at presentation compared to adult-onset SLE	1	A
More severe with increased damage accrual compared to adult-onset disease	2	B
Similar monitoring with adults	3	C
Similar treatment with adults	3	C
Importance of coordinated transition programme to adult specialists	–	C

*Quality of evidence was graded 1–4 and the strength of statements was graded A–C (refer to web-only appendix table 1 for details).
†MPA refers to either mycophenolate mofetil (MMF) or enteric-coated MPA sodium at equivalent dose based on evidence for comparable efficacy of the two regimens. MMF has been used in most controlled trials in LN.
dsDNA, double-stranded DNA; GFR, glomerular filtration rate; UPCR, urine protein:creatinine ratio.

Treatment of adult LN

Initial treatment

Patients with LN should be managed, if possible, in experienced centres.[40] Early trials of immunosuppressive agents have highlighted the importance of long-term (beyond 5 years) follow-up in demonstrating differences in 'hard' outcomes such as doubling of serum creatinine, end-stage renal disease (ESRD) and death.[41–43] Such outcomes, however, are not frequent and may occur late in the course of LN. Intermediate outcome measures, such as renal response and flares, occurring in the majority of patients within the first 2 years after treatment initiation, correlate with hard outcomes in studies with long-term follow-up and are commonly used as endpoints in trials.[9 33–35 37–39 44] Correlation does not guarantee surrogacy of these outcomes for all patients, some of whom may still have hard outcomes diverging from their intermediate outcomes.

To date, long-term data are not available for MPA (box 1). Nonetheless, the publication of the Aspreva Lupus Management Study (ALMS) trial,[45] the largest trial in LN showing comparable response rates between MPA (target mycophenolate mofetil (MMF) dose 3 g/day) and intravenous cyclophosphamide (CY) (monthly pulses 0.5–1 g/m^2), both administered for 6 months, together with the ease of administration and the more favourable gonadal toxicity profile of the former,[46–48] formed the basis for recommending MPA as initial treatment for most cases of class III–IV LN. Evidence from transplantation medicine[49 50] and a single randomised controlled trial (RCT) in LN[51] suggests that MMF and enteric-coated mycophenolic acid sodium (eMPA) are likely to be equally efficacious. To this end, and while awaiting further validation, the Committee felt that either MPA formulation can be used in treatment of LN, with 720 mg dose eMPA roughly equivalent to 1 g dose of MMF. We also recommend low-dose intravenous CY (total dose 3 g over 3 months) in combination with glucocorticoids (0.5 mg/kg/day) as initial treatment of class III–IV (±V) LN in Caucasians based on better efficacy/toxicity ratio than high-dose intravenous CY.[44 52]

A single RCT in patients with pure class V LN demonstrated that the combination of glucocorticoids with intravenous CY (6 bimonthly pulses 0.5–1 g/m^2) was more efficacious than glucocorticoids alone; the combination of glucocorticoids with ciclosporin was also efficacious but was associated with significantly more relapses of nephrotic syndrome than CY.[53] Moreover, combined analysis of two other RCTs in the subgroup of patients with pure class V LN showed a comparable antiproteinuric effect of MPA versus high-dose intravenous CY.[54] By extrapolation from these studies, and based on the more favourable gonadal toxicity profile of MPA compared to CY, we recommend MPA as initial treatment for most cases of class V LN and nephrotic-range proteinuria. The low-dose CY regimen has not been tested in pure class V LN.

Subgroup analysis suggests that MPA may have greater efficacy in patients of African descent;[45 55] further confirmation is needed before issuing a recommendation favouring MPA in these patients. Post hoc analysis in 32 patients in ALMS with baseline GFR<30 ml/min/1.73 m^2,[45] and evidence from 2 controlled studies in severe histological forms of LN,[56 57] support the use of MPA in patients with impaired renal function or crescents. Only high-dose intravenous CY has demonstrated efficacy in a RCT specifically designed to include severe nephritic cases with GFR 25–80 ml/min or with crescents/necrosis in >25% of glomeruli.[58] Data from a RCT[59] and the 10-year follow-up[60] suggest that azathioprine can be used in class III–IV LN albeit at an increased risk for renal relapse (HR 4.5), thus the committee recommends it for milder cases (preserved renal function and no adverse histological findings).

Intravenous methylprednisolone (MP) pulses are recommended as part of the initial treatment regimen by extrapolation from controlled studies,[43 52 61 62] to decrease cumulative glucocorticoid dose and associated harms. Higher initial glucocorticoid dose (oral prednisone 0.7–1 mg/kg/day) may be used in severe renal or extra-renal lupus, or when intravenous MP treatment is not feasible. Clinical experience suggests that a further course of three intravenous MP pulses can be considered in patients failing to improve within the first 3 months.

For class II LN with proteinuria >1 g/24 h despite renin-angiotensin-aldosterone system (RAAS) blockade, especially in the presence of glomerular haematuria, we recommend low-to-moderate doses of glucocorticoids (prednisone 0.25–0.5 mg/kg/day) alone or in combination with azathioprine (1–2 mg/kg/day), if needed, as steroid-sparing agent. Glucocorticoids alone or in combination with immunosuppressive agents may also be considered in cases of class I LN with podocytopathy on the electron microscopy (minimal change disease)[63 64] or interstitial nephritis.[65 66]

Subsequent treatment

For patients improving after initial treatment, we recommend subsequent immunosuppression to consolidate renal response and prevent flares. Although among patients from European ancestries azathioprine and MPA were equivalent after initial treatment with low-dose intravenous CY,[67] a larger RCT suggested a difference between the two drugs in favour of MPA after initial response to either MPA or intravenous CY (monthly pulses 0.5–1 g/m^2).[68] In this trial, sequential use of azathioprine after MPA resulted in more treatment failures as compared to

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Box 1	Research agenda

- Special training sessions for renal pathologists to improve the interpretation of renal biopsy findings in lupus nephritis (LN) and enhance interobserver agreement
- Development and validation of biomarkers which will better reflect kidney biopsy findings and renal disease activity and severity
- Long-term (beyond 5 years) efficacy and safety data for mycophenolic acid
- Provide data to guide duration of immunosuppressive treatment beyond 3 years
- Define the role of adding calcineurin inhibitors, rituximab or belimumab to standard immunosuppressive treatment in cases with residual renal disease
- Need for more data on switching regimens in cases of treatment failure
- Larger studies with extended follow-up are needed to assess the prognostic significance of anti-phospholipid syndrome (APS)-associated nephropathy (APSN) and coexistence of anti-phospholipid antibodies in LN
- Need for controlled trials to assess the role of antiplatelet/anticoagulant regimes in APSN
- Need for randomised controlled trials (RCTs) in paediatric LN and the need to have very long follow-up (beyond 10–15 years) to fully assess the impact of the various treatment strategies and modalities in children

MPA followed by MPA. The committee therefore recommends continuation of MPA if the drug was successful as initial treatment. Calcineurin inhibitors can be considered in selected cases with preserved renal function based on evidence from RCTs.[69–71] Intravenous CY, pulsed every 3 months, may be used in selected cases[43 58 72] but exposure to CY should be minimised, especially in women at risk for amenorrhoea and infertility[73] or men planning to father children.

There is no data to guide duration of treatment beyond 3 years;[67 68] continuing treatment for longer time periods should be individualised with an effort first to withdraw glucocorticoids before immunosuppressive agents. Gradual drug dosage titration may be attempted to ensure the best possible efficacy/toxicity ratio. MPA dose often needs titration to reduce toxicity (doses 1–2 g/day can be effective for long-term treatment). Monitoring MPA blood levels to minimise harm and increase efficacy is under investigation[74–76] but it should be considered in cases with GFR <30 ml/min.

Refractory disease

Complete renal response can take up to 2 years to reach with <30% to 40% of patients achieving this outcome within the first 6 months of treatment.[48 59] Switching to an alternative agent is recommended for patients who fail to improve within 3–4 months, or do not achieve partial response after 6–12 months, or complete response after 2 years of treatment. For patients not responding to MPA or CY, evidence from uncontrolled studies suggests that treatment may be switched from MPA to CY, from CY to MPA,[77 78] or that rituximab (anti-CD20 mAb) may be given either as add-on treatment or as monotherapy.[79 80] Additional options include calcineurin inhibitors (ciclosporin A, tacrolimus),[81–83] intravenous immunoglobulin,[84] plasma exchange for rapidly progressive glomerulonephritis,[49 85] or immunoadsorption for patients who have failed or cannot tolerate other treatments.[86 87] Data on leflunomide are limited.[88]

Adjunctive treatment in patients with LN

We recommend control of cardiovascular disease risk factors in a manner similar to patients who do not have SLE with chronic kidney disease, although benefit has not been demonstrated specifically in SLE.[89] Complications of chronic renal insufficiency (anaemia, cardiovascular disease, metabolic bone disease) should also be managed as in patients who do not have SLE. RAAS blockers are recommended as preferred treatment in all patients who are not pregnant with significant proteinuria or hypertension, based on: (a) evidence for their antihypertensive, antiproteinuric and renoprotective effect,[90–92] and, (b) lack of data on the comparative efficacy of other classes of antihypertensive agents in LN. Their dose is titrated for maximum antiproteinuric effect while monitoring blood pressure (target level <130/80 mm Hg), serum potassium and GFR levels. Epidemiological studies[93 94] and the follow-up of a controlled trial[95] demonstrate that hydroxychloroquine use is associated with higher rates of renal response, fewer renal relapses and reduced accrual of renal damage. Hydroxychloroquine (6.5 mg/kg/day or 400 mg/day, whichever is lower) is generally safe in patients with normal baseline ophthalmological examination; dose adjustments may be necessary in patients with GFR <30 ml/min. Annual ophthalmological screening begins after 5 years of treatment or sooner if there are risk factors for retinal damage.[96] Patients should also be immunised with non-live vaccines according to the EULAR recommendations.[97 98]

Monitoring and prognosis of LN

Patients should be monitored regularly according to EULAR recommendations,[99] including annual examination of cervicovaginal smear in women[100 101] and measurement of serum immunoglobulins at baseline and then annually in patients who receive immunosuppressive treatment to assess risk of infection. Monitoring of body weight, blood pressure, serum creatinine and estimated GFR, serum albumin, proteinuria, urinary sediment (microscopic evaluation), serum C3/C4, serum anti-dsDNA antibody levels and complete blood cell count are used to define activity and evaluate response to treatment although their individual predictive value for hard outcomes at particular time points is modest.

Spot UPCR measured on first morning void urine sample is a valid and conveniently repeatable measure for measuring proteinuria in children and monitoring within-patient changes in adults.[102–104] Timed (12 h or 24 h) urine collections may also be considered at baseline and when major therapeutic changes are considered. Reappearance of urine cellular casts has >80% sensitivity and specificity for renal flares.[105]

Although serum C3 has generally higher sensitivity than serum C4 (72% to 85% vs 28% to 74%), both tests have modest specificity for active LN.[106 107] The diagnostic accuracy of serum anti-dsDNA is also modest with positive and negative likelihood ratios ranging from 1.5–4.8 and 0.3–0.8, respectively. Farr and ELISA methods are both acceptable, although the former yields higher sensitivity and specificity rates.[106 108–110] Anti-C1q[106 111] and anti-nucleosome[112–114] antibodies have higher sensitivity and specificity for active nephritis but further standardisation and validation are required. Changes in serological tests are more important predictors of concurrent or impending LN flare than their absolute levels but should be repeated no more than monthly. In the absence of proteinuria, active serology (decreasing C3/C4 and/or increasing anti-dsDNA) and/or urine sediment is not an indication for pre-emptive treatment but dictates closer monitoring of patients. Repeat renal biopsy provides additional prognostic information[115–118] and can assist therapeutic decisions in patients with relapse of nephritis after complete renal response, or with refractory disease. It can also be used in the context of a clinical trial to monitor treatment efficacy and changes in chronicity scores.[8 119]

Management of ESRD in LN

Despite immunosuppressive treatment, 10% to 30% of patients with LN will progress to ESRD within 15 years of diagnosis. Infections (including peritonitis) may occur in patients with active disease still on immunosuppressive treatment, and contribute to morbidity and mortality.[120–123] Although clinical and serological activity tend to subside in most patients with ESRD on dialysis,[120 124–126] flares of renal or extra-renal lupus can occur.[127–130]

Comparative studies[131 132] and cases series[133 134] support that patients with SLE are good candidates for renal transplantation performed when clinical (and ideally, serological) lupus activity is absent, or at a low level, for at least 3–6 months[135]; best results are obtained with living donor[136–138] and pre-emptive transplantation.[139] Patients with moderate to high titres of antiphospholipid antibodies are at increased risk for thrombotic complications and may receive anticoagulants perioperatively.[140–143] Post-transplantation recurrent LN, although difficult to treat, is a rare cause of renal allograft loss.[136 144 145]

Anti-phospholipid syndrome (APS)-associated nephropathy (APSN) in SLE

Anti-phospholipid antibodies (anti-cardiolipin antibodies, anti-β2-glycoprotein I antibodies, lupus anticoagulant) may be associated with a distinct type of vascular nephropathy (APSN) with adverse prognostic factors such as hypertension, impaired renal function and interstitial fibrosis.[146–149] Histological lesions of APSN are present in 20% to 30% of patients with SLE[146] [150] and include thrombotic microangiopathy and chronic lesions such as fibrous intimal hyperplasia, organising thrombi with recanalisation, focal cortical atrophy and fibrous occlusions of arteries/arterioles, thus, need to be distinguished from thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome and malignant hypertension. In spite of lack of evidence from controlled studies, hydroxychloroquine and/or antiplatelet/anticoagulant treatment can be considered in combination with immunosuppressive treatment if nephritis is present. Patients with definite APS should receive anticoagulation treatment.[151]

LN and pregnancy

Pregnancy may be planned in patients with inactive lupus and UPCR <50 mg/mmol for the preceding 6 months, with GFR that should preferably be >50 ml/min. Patients with LN who are pregnant should ideally be followed by a multidisciplinary team. Stable renal disease is treated with the same drugs that are recommended as acceptable during prepregnancy counselling (hydroxychloroquine, prednisone, azathioprine). Hydroxychloroquine should be continued[152] [153] or even instituted if immunosuppressive agents need to be stopped. MPA or CY should not be used in the last 3 months, and biological agents for at least 4 months—dependent upon the agent used before conception. Blood pressure should be controlled without RAAS blockers at the time of conception if possible, due to their potential teratogenic effect during the first trimester, or with switching to other agents such as nifedipine or labetalol as soon as pregnancy is confirmed.[154] [155] Acetyl-salicylic acid is recommended to reduce the risk for pre-eclampsia.[156] Patients with APS are at increased risk for adverse pregnancy outcomes[154] [157] [158] and should be considered for anticoagulation with low-molecular-weight heparin and/or acetyl-salicylic acid depending on their history of obstetric and/or thrombotic events.[151] Warfarin must be discontinued as soon as pregnancy is confirmed. Patients with nephrotic-range proteinuria are also candidates for anticoagulation.

For monitoring, any fall in serum C3/C4 is significant given than levels usually rise during pregnancy;[159] additional investigation may be needed to rule out pre-eclampsia before diagnosing exacerbation of renal disease.[160] For active disease or pre-eclampsia, combined care with obstetricians is recommended.[158] Close surveillance for renal flare post partum is essential. In addition to acceptable medications used in stable LN, refractory cases can also be treated with calcineurin inhibitors, intravenous immunoglobulin, immunoadsorption and possibly plasma exchange, according to disease severity.[156] [161]

Management of paediatric LN

Children are at increased risk for renal involvement compared to adults with SLE (OR 1.5–2.4), and nephritis often is a presenting feature of paediatric SLE. Together with elevated blood pressure, fever, lymphadenopathy, skin and joint manifestations,[162] children with LN tend to have more active disease over time, receive more intensive immunosuppressive treatment and accrue more damage, often related to glucocorticoid toxicity, compared to adults.[163–168] The diagnosis, management and monitoring is based on extrapolation from evidence in adults, and on the limited, non-randomised, evidence in children with LN.[169–172] Additional considerations include the negative effect of disease activity and glucocorticoids on linear growth, and the modification of body image induced by treatment. This may represent major psychological burden especially in adolescents building their self-esteem and affecting treatment compliance.

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