Chapter 12: Lupus nephritis

Kidney International Supplements (2012) **2,** 221–232; doi:10.1038/kisup.2012.25

INTRODUCTION

This chapter makes treatment recommendations for LN in adults and children. The cost implications for global application of this guideline are addressed in Chapter 2.

BACKGROUND

Kidney involvement in systemic lupus, known as LN, is most often due to glomerular immune complex accumulation, which leads to glomerular inflammation and, if unchecked, also involves the renal interstitium. The kidney may also sustain damage by other mechanisms, such as thrombotic microangiopathy. Lupus patients with LN have worse outcomes than those with no kidney involvement.[586–588] This poor prognosis is explained only in part by the risk of CKD and ESRD, suggesting that LN is a manifestation of a more severe form of systemic lupus.

The reported incidence of clinically important kidney disease in systemic lupus is about 38%. Of those who develop clinical LN, 40–60% have overt kidney disease at the time lupus is diagnosed.[589–591] The incidence of kidney involvement differs with ethnicity. Caucasians (European, European Americans; 12–33%) are less likely to have LN than black (African American, Afro-Caribbean; 40–69%), Hispanic (36–61%), or Asian (Indian, Chinese; 47–53%) patients.

Based on the United States Renal Data Service database, between 1996 and 2004 the incidence of ESRD attributed to LN in adults was 4.5 cases per million in the general population,[592] but was greater in blacks (17–20/million) and Hispanics (6/million) than Caucasians (2.5/million). Similarly, a retrospective cohort from the UK found that 19% of Caucasians and 62% of blacks with LN progressed to ESRD.[593] In a Saudi Arabian population, 12% of patients with LN developed ESRD.[589,594] The prevalence of CKD in patients with systemic lupus is difficult to estimate, but because current therapies induce complete remission in only about 50% of those with LN, CKD is likely to be common.

The presence of LN should be considered in any lupus patient with impaired kidney function, proteinuria, hypertension, or an active urine sediment. An active sediment includes hematuria, especially acanthocytes suggestive of glomerular bleeding, leukocyturia in the absence of infection, and red and white blood cell casts. LN must be confirmed by kidney biopsy. The histologic findings provide the basis for treatment recommendations for LN.

12.1: Class I LN (minimal-mesangial LN)

12.1.1: We suggest that patients with class I LN be treated as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

BACKGROUND

In class I LN, glomeruli are normal by light microscopy. Class I LN is defined by the presence of immune deposits restricted to the mesangium, and seen only by immunofluorescence or electron microscopy.

RATIONALE

- Class I LN has no clinical kidney manifestations.
- Class I LN is not associated with long-term impairment of kidney function.

Kidney tissue obtained for research purposes in patients with systemic lupus but without clinical signs of kidney disease showed LN was present in about 90% of patients,[595,596] far more than the 40% or so who manifest clinical kidney disease. In some patients with clinically silent class I LN, there is transformation to more aggressive and clinically relevant forms of LN.[597] However, at present, there are no data to suggest that every patient with lupus requires a kidney biopsy, or that treatment of class I LN is clinically necessary.

12.2: Class II LN (mesangial-proliferative LN)

12.2.1: Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

12.2.2: We suggest that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (see Chapter 5). (*2D*)

BACKGROUND

The kidney biopsy of class II LN shows mesangial hypercellularity and matrix expansion on light microscopy, and mesangial immune deposits by immunofluorescence and electron microscopy. Clinically, proteinuria and/or hematuria may be seen in class II LN, but usually not nephrotic syndrome, or kidney impairment. If nephrotic-range proteinuria is found with class II LN, this may be due to a concomitant podocytopathy.

RATIONALE

- There are no evidence-based data on the treatment of class II LN.
- Podocytopathies, characterized histologically by diffuse foot process effacement in the absence of glomerular capillary wall immune complex deposition or endocapillary proliferation, have been observed in patients with class II LN.

Podocyte injury in class II LN does not appear related to the extent of mesangial immune complex deposition.[598] While there have been no prospective studies of the treatment of nephrotic-range proteinuria in class II LN, it is reasonable to treat such patients as for MCD/FSGS in case of nephrotic syndrome, or if proteinuria cannot be controlled using RAS blockade.

12.3: Class III LN (focal LN) and class IV LN (diffuse LN)—initial therapy

12.3.1: We recommend initial therapy with corticosteroids (*1A*), combined with either cyclophosphamide (*1B*) or MMF (*1B*).

12.3.2: We suggest that, if patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (*2D*)

BACKGROUND

Class III and IV LN are differentiated by the percentage of affected glomeruli (class III, $<50\%$; class IV, $\geq 50\%$). Glomerular lesions are classified as active (A) or chronic (C). The active lesions of class III and IV are endocapillary and (usually) mesangial hypercellularity, crescents, necrosis, wire loops, and hyaline thrombi. Chronic lesions include segmental and global glomerulosclerosis. Immunofluorescence and electron microscopy show significant subendothelial and mesangial immune deposits. If there are extensive subepithelial immune deposits, there is coincidental class V LN (see Rationale).

Almost all patients will have microscopic hematuria and proteinuria; nephrotic syndrome and kidney impairment are common. However, if the histologic lesions are mainly chronic (see Rationale) there may be less overt clinical activity, other than progressive kidney failure. Therapy should be adjusted according to the extent of activity or chronicity.

There is no standard definition of treatment response for class III and IV LN, which makes direct comparison of clinical trials difficult. Nonetheless, the overall goals of treatment are similar between trials, and definitions of response based on published trials are provided as a guide to the success of therapy (Table 27).

Table 27 | Definitions of response to therapy in LN

Complete response: Return of SCr to previous baseline, plus a decline in the uPCR to <500 mg/g (<50 mg/mmol).

Partial response: Stabilization ($\pm 25\%$), or improvement of SCr, but not to normal, plus a $\geq 50\%$ decrease in uPCR. If there was nephrotic-range proteinuria (uPCR ≥ 3000 mg/g [≥ 300 mg/mmol]), improvement requires a $\geq 50\%$ reduction in uPCR, and a uPCR <3000 mg/g [<300 mg/mmol].

Deterioration: There is no definition of deterioration in LN to define treatment failure that has been tested prospectively as an indication to change in initial therapy. A sustained 25% increase in SCr is widely used but has not been validated.

RATIONALE

- Proliferative LN (class III or IV) is an aggressive disease.
- Before 1970, kidney survival and overall patient survival in diffuse proliferative LN were very poor, in the range of 20–25%.
- Patient and kidney survival in class III and IV LN have dramatically improved through the use of intensive immunosuppression.
- The International Society of Nephrology/Renal Pathology Society classification of LN assigns activity (A) or chronicity (C) in class III and IV LN. Our treatment recommendations are for active or active plus chronic lesions. Thorough review with the nephropathologist is required to ensure accurate classification prior to starting therapy.
- Therapy for class III and IV LN has initial and maintenance phases. The objective is to rapidly decrease kidney inflammation by initial intensive treatment, and then consolidate treatment over a longer time. The initial phase is often called induction, which implies remission is achieved at its completion. This, however, is often not the case, and remissions continue to occur well into the maintenance phase. The term "initial" treatment is therefore preferred.
- The benefit of the addition of cyclophosphamide to corticosteroids for initial treatment was shown in controlled trials demonstrating that, during long term follow-up, this combination decreased the frequency of kidney relapse, CKD, and ESRD compared to corticosteroids alone.
- The evolution of initial therapy in proliferative LN has been to reduce toxicity while maintaining efficacy. This has resulted in several modifications of cyclophosphamide dosing, and the introduction of MMF as an alternative to cyclophosphamide.
- The efficacy of newer initial treatment regimens should be assessed not only by initial responses, but also by long-term effects on kidney relapse, and development of CKD.

Widely used treatment regimens are shown in Table 28.

Increases in disease activity in systemic lupus in general, and in LN in particular, may be described as "flares" or "relapses". In this guideline, we use the term "relapse".

Corticosteroids

All regimens use similar corticosteroid dosing: an initial dose of oral prednisone up to 1 mg/kg, tapering according to clinical response over 6–12 months. Additional i.v. methylprednisolone is widely used at the beginning of treatment for more severe disease. However, the dosing and duration of corticosteroids has never been subject to evaluation by RCTs.

Cyclophosphamide

i.v. cyclophosphamide (0.5–1 g/m^2) given monthly for 6 months (Regimen A, sometimes called the "NIH regimen") was the first immunosuppressive treatment shown in RCT to be superior to corticosteroids alone.[599–602]

Table 28 | Regimens for initial therapy in class III/class IV LN

Regimen	A. NIH	B. Euro-Lupus	C. Oral cyclophosphamide	D. MMF
Cyclophosphamide	i.v. cyclophosphamide 0.5–1 g/m^2; monthly for 6 months	i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months	Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months	—
MMF	—	—	—	MMF up to 3 g/d for 6 months
Benefit shown by RCT in proliferative LN	Yes	Yes	Yes	Yes
Benefit shown by RCT in severe proliferative LN	Yes	Untested	Untested	Untested
Comments	Effective in whites, blacks, Hispanics, Chinese	Effective in whites. Untested in blacks, Hispanics, Chinese	Effective in whites, blacks, Chinese; easy to administer and lower cost than i.v. cyclophosphamide	Effective in whites, blacks, Hispanics, Chinese; high cost

LN, lupus nephritis; MMF, mycophenolate mofetil; RCT, randomized controlled trial.
All regimens include corticosteroids:
- Oral prednisone, initial dose up to 0.5–1 mg/kg/d, tapering over 6–12 months according to clinical response.
- i.v. methylprednisolone is sometimes added initially for severe disease.

A lower-dose regimen using i.v. cyclophosphamide 500 mg every 2 weeks for 3 months (Regimen B, sometimes called the "Euro-Lupus regimen") had equivalent efficacy to Regimen A in an RCT in Caucasians.[603,604] However, few patients in the Euro-Lupus trial had severe kidney disease, defined as rapidly progressive kidney failure and typically with widespread ($>50\%$) segmental glomerular necrosis or crescents. It remains uncertain whether Regimen B has equivalent efficacy to Regimen A in severe class III/IV LN, and in patients of other ethnicities.

Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months (Regimen C) has been used as an alternative to i.v. cyclophosphamide.[605,606] It has equivalent efficacy to i.v. cyclophosphamide in prospective observational studies,[599,607–610] and has also been shown equivalent to mycophenolate in Chinese patients,[611,612] although this has not yet been verified in other ethnicities. More adverse effects have been reported with oral compared to i.v. cyclophosphamide, but this is not a consistent finding.

Mycophenolate

MMF (maximum 3 g/d) for 6 months (Regimen D) has been tested in an RCT in a Chinese population, and was equivalent in achieving remission to Regimen C; patients with severe LN were excluded from this study.[612]

An RCT known as the Aspreva Lupus Management Study (ALMS)[613] recruited 370 patients with class III, IV, and V LN, and comparing MMF to Regimen A, showed that MMF had an equivalent response rate to i.v. cyclophosphamide at 6 months, and had a similar incidence of adverse events including serious infections and deaths.[613]

Enteric-coated mycophenolate sodium may also be effective in LN, as suggested by a small trial in cyclophosphamide resistant patients.[614]

Other regimens

There is more limited RCT evidence for the use of three other regimens as initial treatment: corticosteroids combined with (i) azathioprine; or (ii) cyclosporine; or (iii) the combination of tacrolimus and MMF (sometimes called "multitarget" therapy).

Azathioprine

An RCT in Europeans compared initial therapy with azathioprine combined with i.v. methylprednisone, followed by oral prednisone, to i.v. cyclophosphamide with oral prednisone.[615] At 2 years, there was no difference in response rate, and fewer adverse effects in those receiving azathioprine. However, supplementary studies in these cohorts showed a higher late relapse rate and higher risk of doubling of SCr after azathioprine. Furthermore, there was more chronicity on later biopsies after azathioprine.[616]

Cyclosporine

A small ($n=40$), open-label RCT compared cyclosporine to cyclophosphamide as initial therapy combined with corticosteroids for proliferative LN.[617] Cyclosporine (4–5 mg/kg/d) was used for 9 months, and then tapered over the next 9 months. Cyclophosphamide was used in a different regimen than in most published trials: eight i.v. pulses (10 mg/kg) were given in the first 9 months, and then four to five oral pulses (10 mg/kg) over the next 9 months. There were no differences in responses or remissions at 9 or 18 months, or relapse rate after 40 months of follow-up. Infections and leukopenia did not differ between the groups.

Tacrolimus with Mycophenolate

In a small RCT from China in patients with combined class IV and V LN, the combination of tacrolimus (4 mg/d), MMF (1 g/d), and oral corticosteroids (sometimes known as "multitarget" therapy) was compared to pulse monthly i.v. cyclophosphamide (0.75 g/m^2 for 6 months) plus oral corticosteroids. At 6 months, 90% of patients treated with this multitarget therapy and 45% of patients treated with cyclophosphamide achieved either complete or partial remission ($P=0.002$).[618] This regimen has not yet been evaluated in other ethnic groups.

The use of cyclophosphamide in the treatment of class III/IV LN became routine after a prospective RCT demonstrated that cyclophosphamide added to corticosteroids reduced development of ESRD.[599] Other studies showed that adding cyclophosphamide to corticosteroids decreased LN relapses, improved remission rate, and decreased development of CKD.[600–602] Retrospective analysis of repeat kidney biopsies from selected patients who had participated in the NIH trials showed that those receiving only corticosteroids had a linear increase in the chronicity index over time (median 44 months after treatment), whereas patients receiving corticosteroids and cyclophosphamide (or other immunosuppressive drugs) had no change in the chronicity index,[619] suggesting the immunosuppressive drugs prevented progressive kidney scarring. A criticism of these studies is the small number of patients, especially during long-term follow-up.

There were no significant differences in outcome between i.v. and oral cyclophosphamide in the original RCT that led to the widespread use of Regimen A,[599] but because bladder toxicity (chemical cystitis) developed only in patients receiving oral cyclophosphamide, i.v. cyclophosphamide became the standard treatment[599] (Online Suppl Tables 78–79). In this initial trial, patients were exposed to large cumulative amounts of cyclophosphamide; oral cyclophosphamide was used at doses up to 4 mg/kg/d for a median of 4 years, far greater than now recommended, and i.v. cyclophosphamide was continued for a median of 4 years. Given the potential for developing hematologic malignancies later in life, these large cumulative doses of cyclophosphamide should be avoided. We suggest a lifetime maximum of 36 g cyclophosphamide in patients with systemic lupus.[13,284] This is reflected in Regimens A–C.

There are other important considerations, when using cyclophosphamide, to reduce its toxicity. The dose of cyclophosphamide should be decreased by 20% or 30% in patients with CrCl 25–50 and 10–25 ml/min, respectively.[620] The dose of i.v. cyclophosphamide should be adjusted to keep the day 10–14 leucocyte count nadir $\geqslant$3000/μl. When using oral cyclophosphamide, white blood cell counts should be monitored weekly and cyclophosphamide dose should be adjusted to keep leucocytes $\geqslant$3000/μl. Leukopenia requires careful evaluation, since systemic lupus, as well as cyclophosphamide, can cause suppression of bone marrow.

To minimize bladder toxicity with oral cyclophosphamide, we suggest instructing patients to take cyclophosphamide in the morning, and to drink extra fluid at each meal and at bed time. The use of sodium-2-mercaptoethane (mesna) will also minimize the risk of hemorrhagic cystitis when cyclophosphamide is given as i.v. pulses.

To protect fertility, women should be offered prophylaxis with leuprolide and men testosterone while cyclophosphamide is being given.[621,622] Administration of leuprolide must be timed carefully in relation to cyclophosphamide to maximize benefit. Ovarian tissue cryopreservation is an additional, but expensive, option. The efficacy of testosterone in preserving fertility in males is poorly established, so sperm banking should be offered.

Given the toxicity of cyclophosphamide, studies were undertaken to determine if the dosing regimen could be modified. An RCT has tested the efficacy of low-dose, short-duration cyclophosphamide (Regimen B) in Caucasians.[603,604] This regimen resulted in a higher percentage of remissions and a lower incidence of severe infections than Regimen A, although the differences were not statistically significant.[604] Importantly, this low-dose cyclophosphamide regimen had similar long-term outcomes (mean follow-up of 10 years) to Regimen A[603] (Online Suppl Table 77). In this trial, the majority of patients were white, and most patients did not have clinically severe disease. Therefore, it is not certain whether this protocol will be effective in patients of other ancestry, or in patients with more severe class III/IV LN.

A cyclophosphamide-free regimen has been proposed (Regimen D). MMF is used for the first 6 months of LN treatment, instead of sequential cyclophosphamide followed by MMF. The basis for this approach was three small studies of MMF in Asia, and one larger study (140 patients) from the USA.[611,623–625] The Asian studies concluded MMF was equivalent to cyclophosphamide, but the USA trial demonstrated MMF was superior to i.v. cyclophosphamide, although many patients did not achieve the target dose of cyclophosphamide, and a significant percentage of patients showed no response or withdrew from the study. An RCT (ALMS)[613] recruited 370 patients with class III, IV, and V LN, giving oral corticosteroids and either daily oral MMF or 6-monthly i.v. pulses of cyclophosphamide (0.5–1 g/m^2). The ALMS trial showed that MMF was equivalent to i.v. cyclophosphamide in inducing a response at 6 months.[613] ALMS showed a similar incidence of adverse events, serious infections, and deaths for MMF and cyclophosphamide (Online Suppl Tables 71–73). Similar results were found in an Egyptian cohort.[626]

A posthoc analysis of the ALMS trial indicated that black, Hispanic, and mixed-race patients, (generally considered to have more resistant LN[627]) had inferior outcomes with cyclophosphamide compared to MMF. Further information is required from RCTs before recommendations can be made about the efficacy of MMF in patients of specific ethnicity.

Because the kidney response rate for class III and IV LN with any of the initial therapies so far discussed is only about 60% at 6–12 months, an RCT adding rituximab or placebo to MMF plus corticosteroids for initial LN therapy was undertaken to determine if remission rates could be improved.[628] This RCT was based on several small, open-label, uncontrolled trials that suggested rituximab may be effective in proliferative LN, either for refractory disease or as initial therapy.[629–635] At 12 months, however, there were no differences between the rituximab and placebo groups in terms of complete or partial remissions. Thus, rituximab cannot be recommended as adjunctive initial therapy.

Choice of Initial Therapy

The patients in the two largest studies of MMF vs. cyclophosphamide generally had less severe LN, assessed by level of proteinuria and kidney function,[613,623] than the patients in some of the RCTs of cyclophosphamide.[601,636] Thus, in severe class III/IV LN, a cyclophosphamide-containing protocol for initial therapy may be preferred. However, a subset of patients in the ALMS trial did have severe LN and responded to MMF, so more data are required. In patients with less severe proliferative LN, an initial regimen not containing cyclophosphamide should be considered.

Additionally, the beneficial effect of cyclophosphamide in preservation of kidney function was only apparent after 3–5 years of follow-up.[599–601] This length of time, which was needed to show a difference between initial therapies in long-term kidney survival, must therefore be kept in mind when evaluating new, non–cyclophosphamide-containing regimens as initial therapy for class III/IV LN. For example, the Dutch Working Party on systemic lupus found that azathioprine, an antimetabolite like MMF, was equivalent to cyclophosphamide as initial therapy of class III and IV LN; however, in the long term, repeat biopsies showed more chronic damage with azathioprine, as well as a higher incidence of kidney relapse and doubling of SCr (Online Suppl Tables 74–76).[615,616] In some regions where cost and drug availability are an issue, it may be necessary to use azathioprine for initial treatment of class III and IV LN.

In a long-term study of continuous MMF therapy compared to initial cyclophosphamide followed by azathioprine, there were no significant differences in kidney function between the groups after a median of 64 months.[612] However, in the MMF group, more patients had relapses, prolonged proteinuria >1 g/d, and persistent SCr >2 mg/dl (>177 μmol/l). These combined clinical findings have been associated, in other studies, with deterioration of kidney function over time.

After the initial 6-month treatment period, the ALMS trial was extended for 3 years to evaluate maintenance therapy with either MMF or azathioprine.[637] Although not designed to compare the long-term efficacy of initial therapy on kidney function, there was a (nonsignificant) trend toward fewer treatment failures in those who received cyclophosphamide as initial therapy as opposed to MMF. This result was independent of whether maintenance therapy was azathioprine or MMF.

Thus, it cannot yet be stated that initial therapy with MMF is equal to cyclophosphamide for proliferative LN with respect to long-term kidney function.

12.4: Class III LN (focal LN) and class IV LN (diffuse LN)—maintenance therapy

12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose oral corticosteroids ($\leq$10 mg/d prednisone equivalent). (*1B*)

12.4.2: We suggest that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (*2C*)

12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (*2D*)

12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)

12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)

RATIONALE

- There is moderate-quality evidence from RCTs in patients with class III/IV LN that prolonged maintenance therapy after initial treatment is required.
- There is moderate-quality evidence that maintenance therapy with azathioprine or MMF is superior to maintenance with cyclophosphamide as judged by risk of death, and risk of development of CKD.
- There is moderate-quality evidence that azathioprine and cyclosporine A have comparable efficacy as maintenance therapies for class III/IV LN.
- There is very low–quality evidence to guide the duration of maintenance therapy after complete remission, but most randomized studies of class III/IV LN have given therapy for several years.

The need for maintenance therapy was suggested when patients treated only with short-term (6 months) i.v. cyclophosphamide therapy were shown to have an increased frequency of kidney relapses.[600]

Choice of Maintenance Therapy

Presently, there are several options for maintenance therapy after the initial treatment of proliferative LN. The data currently available do not allow a definitive recommendation as to the choice of agent for maintenance therapy, although in a multiethnic cohort MMF was superior to azathioprine. Patient-specific factors, such as desire for pregnancy or occurrence of side-effects, should however be considered when making this choice.

A cohort of mainly black and Hispanic patients with class III/IV LN was treated with monthly i.v. cyclophosphamide for up to seven cycles, followed by azathioprine or MMF, and compared to patients treated with 6-monthly cyclophosphamide pulses followed by quarterly cyclophosphamide

pulses for 1 year beyond remission.[638] This study showed that, over 72 months, the patients treated with maintenance azathioprine or MMF were significantly less likely to reach the composite end-point of death or CKD than the cyclophosphamide maintenance group, and to experience fewer adverse effects.

The MAINTAIN Nephritis Trial compared MMF with AZA as maintenance therapy in a predominantly Caucasian population after initial treatment with low-dose (Regimen B) cyclophosphamide.[639] They had not necessarily achieved remission after initial therapy. The primary end-point was time to kidney relapse. After at least 3 years of follow-up, this trial found MMF and azathioprine to be equivalent.

The ALMS trial extension phase[637] compared MMF and AZA as maintenance therapies after the 6-month initial treatment period (Regimen D). Patients entered this extension phase only if they achieved a complete or partial remission after initial therapy. Over 3 years, the composite treatment failure end-point (death, ESRD, kidney flare, sustained doubling of SCr, or requirement for rescue therapy) was reached in 16% of MMF-treated patients compared to 32% of azathioprine-treated patients ($P = 0.003$). The superiority of MMF over azathioprine was not dependent on initial therapy or race of the patient.

A pilot RCT in 69 patients with class III/IV LN suggested that 2 years of cyclosporine may be as effective as 2 years of azathioprine for maintenance, after initial treatment with prednisone and oral cyclophosphamide, in terms of relapse prevention and reduction of proteinuria.[606] Another RCT showed cyclosporine was as effective as azathioprine in terms of tapering maintenance corticosteroids in severe systemic lupus, but only 29% of the patients had LN.[640]

Duration of Therapy

Few patients reach complete remission by 6 months, and kidney biopsies after 6 months of initial therapy have shown that, while active inflammation tends to improve, complete resolution of pathologic changes is unusual.[614,625,641,642] Consistent with this finding, clinical improvement in class III/IV LN continues well beyond 6 months and into the maintenance phase of therapy.[603,605,607,610,615,643] Decisions to alter therapy should not be based on urine sediment alone. A repeat kidney biopsy may be considered if kidney function is deteriorating.

There is no evidence to help determine the duration of maintenance therapy. The average duration of immunosuppression was 3.5 years in seven RCTs.[599,600,603,604,609,612,615,638] We suggest that immunosuppressive therapy should usually be slowly tapered after patients have been in complete remission for a year. If a patient has a history of kidney relapses it may be prudent to extend maintenance therapy.

Immunosuppression should be continued for patients who achieve only a partial remission. However, the strategy of trying to convert a partial remission to a complete remission by increasing corticosteroids or using alternative immunosuppressive agents is not supported by evidence.

There are few data on repeat biopsies after therapy. Biopsies taken two or more years after initial therapy often continue to show activity, especially when there is still significant proteinuria or an abnormal SCr.[644] Of more concern, one study found that, in patients with initial class III and IV LN, only 40% had reverted to class II LN on repeat biopsy after 2 years of immunosuppressive therapy.[616] The SCr and extent of proteinuria at the time of the second biopsy did not differentiate between the group that reverted to class II and the group that remained with class III or IV LN.

Predictors of Response to Treatment of Class III/IV LN

Reported response rates are affected by variability in the definition of remission and variability of initial treatment regimens. Although complete remission should be the goal for LN, attaining at least a partial remission significantly improves kidney prognosis and patient mortality compared to no remission.[645]

The 6- to 12-month response rates (both complete and partial) from several trials involving black, white, Hispanic, Mexican, and mixed-race patients are between 20% and 85%.[604,605,613,615,623,638] Complete remission rates at 6–12 months were between 8% and 30% in these studies. In contrast, Chinese patients in clinical trials had a consistently better response rate of about 90% and a complete remission rate of 60–80%.[607–609,611]

Multivariate analyses of retrospective studies suggest that the most important predictors for not achieving remission are SCr at the start of treatment (RR 0.21 per 1 mg/dl [88 μmol/l]), the magnitude of increase in SCr during relapse, a delay in starting therapy for more than 3 months after a clinical diagnosis of LN, and severity of proteinuria (HR 0.86 per 1 g/d proteinuria [uPCR 1000 mg/g or 100 mg/mmol]).[627,643]

In one prospective study there were no clinical variables predictive of achieving remission on multivariate analysis,[609] while another prospective study showed initial SCr was a predictor of complete remission (RR = 0.96 per μmol/l [0.0113 mg/dl] increase in SCr).[608]

Multivariate analysis from a prospective study showed that failure to achieve complete remission was a major risk factor for kidney relapse,[607] while other studies found that no variables were independently predictive of relapse.[616] A survey of several retrospective studies shows that the one common predictor for risk of CKD, ESRD, or death is SCr at presentation.[627,646–648] In children with LN, failure to respond to therapy and kidney relapse were risk factors for ESRD, HR 5.5 and 11.8 respectively.[649]

Monitoring Therapy of Class III/IV LN

The progress of LN therapy is monitored with serial measurements of proteinuria and SCr. There are not yet any more sensitive biomarkers of kidney response in lupus of proven clinical value.[650] In LN, as in other proteinuric GN, resolution of proteinuria is the strongest predictor of kidney survival;[477,651,652] thus, effective treatment is expected to decrease proteinuria over time.

Effective therapy is also expected to result in reduction of an elevated SCr. A caveat is that there may be may be an acceptable increment in SCr in association with concomitant RAS blockade. Urine sediment should be monitored serially during LN therapy, specifically looking for resolution of cellular casts over time. However, hematuria may persist for months even if therapy is otherwise successful in improving proteinuria and kidney dysfunction. It is desirable to see serologic markers of lupus activity, such as complement and double-stranded DNA antibody levels, normalize with treatment. However, C3 and C4, and anti–double-stranded DNA antibodies have low sensitivity (49–79%) and specificity (51–74%) in relationship to LN activity.[653–659]

RESEARCH RECOMMENDATIONS

- RCTs are needed to compare the efficacy of MMF and cyclophosphamide as initial therapy in non-Caucasian patients.
- RCTs are needed to examine steroid-free and steroid-limited regimens.
- An RCT is needed to determine the duration of maintenance therapy in proliferative LN after complete remission.
- Studies are needed to determine if repeat biopsy of patients who achieve only partial remission can guide therapy to achieve complete remission.
- Biomarkers need to be identified that reflect response to therapy and kidney pathology. These would then need to be tested to determine whether they could be used to guide treatment withdrawal, re-treatment, and change in treatment.

12.5: Class V LN (membranous LN)

12.5.1: We recommend that patients with class V LN, normal kidney function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

12.5.2: We suggest that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide (*2C*), or CNI (*2C*), or MMF *(2D*), or azathioprine (*2D*).

BACKGROUND

In class V LN, light microscopy typically shows thickened glomerular basement membranes; immunofluorescence and electron microscopy show only subepithelial immune complexes. If class V LN is accompanied by endocapillary hypercellularity and/or subendothelial immune deposits, this adds class III or IV to the histologic diagnosis. In class V LN, the main clinical finding is proteinuria, often nephrotic-range, with or without hematuria; kidney function is usually normal. If class III or IV LN is also present, urine sediment may be more active, and kidney impairment is more likely.

RATIONALE

- Pure class V LN, although regarded as indolent compared to class III and IV LN, is still associated with the development of CKD and ESRD, especially if there is heavy proteinuria.
- Nephrotic-range proteinuria in class V LN generally does not spontaneously remit.
- There has only been one small RCT in class V LN, which compared corticosteroids plus immunosuppression to corticosteroids alone.
- There have been a few small, retrospective trials of MMF and azathioprine in class V LN.
- There have been no studies of the effect of treatment of class V LN on long-term kidney outcomes.
- The prognosis for patients with mixed membranous and proliferative lesions [i.e., class V plus class III or IV LN] is less favorable than pure class V LN, and similar to that of patients with class III or IV LN. Patients with mixed membranous and proliferative lesions should be treated similarly to those with class III and IV LN.

There are no convincing data to treat class V LN and subnephrotic proteinuria with immunosuppression; however, given the adverse effects of proteinuria on the kidney, it is reasonable to treat these patients with antiproteinuric and antihypertensive medications (see Chapter 2). These therapies may reduce proteinuria by as much as 30–50% in class V LN.[486,652,660] They should also be used as an adjunct to immunosuppression for patients with nephrotic-range proteinuria.

The justifications to treat class V LN and nephrotic proteinuria with immunosuppression are as follows. Decreased GFR occurs in about 20% of cases of class V LN, and ESRD in about 8–12% after 7–12 years,[661–664] with one study reporting death or ESRD in 28% of patients at 10 years.[665] Spontaneous remission of heavy proteinuria occurs in only a minority of class V LN.[666,667] The adverse effects of sustained, heavy proteinuria include hyperlipidemia and atherosclerosis, contributing to cardiovascular morbidity and mortality,[652,668] and hypercoagulability with arterial and venous thromboses.[588,652] Thrombotic events occur in 13–23% of class V LN, and have been associated with antiphospholipid antibodies, and/or the nephrotic syndrome.[661,664,669]

There is only one small RCT ($n = 15$ in each treatment arm) examining the treatment of class V LN.[670] This study compared the addition of cyclophosphamide or cyclosporine to prednisone in a USA cohort that included blacks, Hispanics, and whites. Both cyclophosphamide and cyclosporine significantly increased response (complete remission 40–50% vs. 14% at 12 months). However, relapse after stopping therapy was much more likely in those treated with cyclosporine (40% within 1 year) compared to cyclophosphamide (no relapse in 48 months). In the same study, the only independent predictor of failure to achieve remission

(by multivariate analysis) was initial proteinuria over 5 g/d. Failure to achieve sustained remission was a risk factor for decline in kidney function (Online Suppl Tables 82–84).

There have been small uncontrolled retrospective, or open-label, studies of MMF and azathioprine with or without corticosteroids in class V LN.[663,669,671,672] In general, these studies have shown complete remission rates of 40–60% at 6–12 months. A small open-label trial of tacrolimus in class V LN showed a complete remission rate of 39% at 6 months.[673] Before these regimens can be recommended, they will need to be tested in RCTs.

Patients with mixed class V and class III or IV LN may have a less favorable prognosis, and should be treated as for the proliferative component.[664]

RESEARCH RECOMMENDATION

- An RCT is needed to compare MMF to cyclophosphamide or a CNI, for induction of remission of pure class V LN.

12.6: General treatment of LN

12.6.1: We suggest that all patients with LN of any class are treated with hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (*2C*)

RATIONALE

- There is low-quality evidence that hydroxychloroquine may protect against the onset of LN, against relapses of LN, ESRD, vascular thrombosis, and that it has a favorable impact on lipid profiles.[674]

In a prospective study, hydroxychloroquine was maintained or withdrawn in a cohort of patients who had been receiving it before the diagnosis of LN.[675] Those who had been on hydroxychloroquine before developing LN had a lower frequency of ESRD, cardiovascular events, and thrombotic events than patients who had never received hydroxychloroquine; HR for ESRD 0.29 (95% CI 0.026–1.009).[676] A large ($n = 1930$), retrospective study found that treatment with hydroxychloroquine protected against vascular thrombosis (OR 0.62; $P < 0.0005$).[677] Finally, in a prospective observational cohort, hydroxychloroquine was shown to retard kidney damage in LN; the cumulative probability of a 50% reduction in GFR or ESRD after 10 years was 38% for patients on hydroxychloroquine and 70% for those who were not ($P < 0.0001$).[678] Patients on hydroxychloroquine should have yearly eye examinations for retinal toxicity, especially after 5 years of continuous use.

12.7: Class VI LN (advanced sclerosis LN)

12.7.1: We recommend that patients with class VI LN be treated with corticosteroids and immunosuppressives only as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

BACKGROUND

In class VI LN, at least 90% of the glomeruli are sclerotic, usually globally, along with interstitial fibrosis and tubular atrophy, with no signs of immunologic activity; the biopsy specimen should be sufficient to be representative of the whole kidney. The dominant clinical picture in class VI LN is severe kidney impairment, usually accompanied by proteinuria and sometimes hematuria.

RATIONALE

- Class VI LN reflects chronic injury, and the consequences of the loss of functional kidney mass, without active immune-mediated injury. Therefore, immunosuppression is not indicated.
- Despite the absence of active LN, patients may still have extrarenal manifestations of systemic lupus requiring immunosuppression.
- As with CKD from any etiology, antiproteinuric and antihypertensive therapies are indicated to preserve residual kidney function and delay ESRD as long as possible.

12.8: Relapse of LN

12.8.1: We suggest that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (*2B*)

12.8.1.1: If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non–cyclophosphamide-based initial regimen be used (Regimen D, Table 28). (*2B*)

12.8.2: Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (*Not Graded*)

RATIONALE

- LN is a relapsing condition.
- Relapses are associated with development of CKD.
- The pathologic findings in LN may change with a relapse, and such changes cannot, with certainty, be predicted clinically.

In subjects with LN who had participated in RCTs, 40% of complete responders experienced a kidney relapse within a median of 41 months after remission, and 63% of partial responders had a kidney flare within a median of 11.5 months after response.[679] The strongest risk factor for relapse is failure to achieve complete remission (HR 6.2).[607]

Relapses are important to recognize and treat, because the kidneys sustain some chronic damage with each relapse that may culminate in CKD, or eventually ESRD. This is

Table 29 | Criteria for the diagnosis and classification of relapses of LN

Mild kidney relapse	Moderate kidney relapse	Severe kidney relapse
Increase in glomerular hematuria from <5 to >15 RBC/hpf, with ≥ 2 acanthocytes/hpf *and/or* recurrence of ≥ 1 RBC cast, WBC cast (no infection), or both	If baseline creatinine is: <2.0 mg/dl [<177 μmol/l], an increase of 0.20–1.0 mg/dl [17.7–88.4 μmol/l] $\geqslant 2.0$ mg/dl [$\geqslant 177$ μmol/l], an increase of 0.40–1.5 mg/dl [35.4–132.6 μmol/l] *and/or* If baseline uPCR is: <500 mg/g [<50 mg/mmol], an increase to $\geqslant 1000$ mg/g [$\geqslant 100$ mg/mmol] 500–1000 mg/g [50–100 mg/mmol], an increase to $\geqslant 2000$ mg/g [$\geqslant 200$ mg/mmol], but less than absolute increase of <5000 mg/g [<500 mg/mmol] >1000 mg/g [>100 mg/mmol], an increase of $\geqslant 2$-fold with absolute uPCR <5000 mg/g [<500 mg/mmol]	If baseline creatinine is: <2 mg/dl [<177 μmol/l], an increase of >1.0 mg/dl [>88.4 μmol/l] $\geqslant 2$ mg/dl [$\geqslant 177$ μmol/l], an increase of >1.5 mg/dl [>132.6 μmol/l] *and/or* an absolute increase of uPCR >5000 mg/g [>500 mg/mmol]

hpf, high-power field; LN, lupus nephritis; RBC, red blood cell; uPCR, urine protein:creatinine ratio; WBC, white blood cell.
Adapted from Lahita RG, Tsokos GT, Buyon JP, Koike T (eds). Systemic Lupus Erythematosus, 5th edn. Rovin BH, Stillman IE. Chapter 42: Kidney. Elsevier: Waltham, MA, 2011, pp 769–814 with permission from Elsevier.[687]

supported by repeat biopsy studies that showed an increase in the chronicity index at the second biopsy, even after successful treatment.[614,616,618,625,641,644,680]

LN may spontaneously transform from one class to another. The most common transformation is from class III to IV.[644] Also, a recent retrospective study found clinically relevant class transformation to be more frequent from a nonproliferative to a proliferative class, rather than proliferative to nonproliferative transformation.[681] Clues to a change in LN class are the development of nephrotic-range proteinuria and changes in the activity of urine sediment, but definitive diagnosis requires a biopsy.

Kidney relapse is diagnosed by clinical criteria based on changes in urine sediment, rate of protein excretion, and SCr change from baseline values in an individual patient. There is no consensus on the definition of a kidney relapse; criteria used in several published studies are shown in Table 29.[682–686] A fall in levels of serum complement components and a rise in anti–double-stranded DNA antibody titers also support a diagnosis of relapse but will not necessarily be present.

RESEARCH RECOMMENDATION

- A study of repeat kidney biopsies at the time of kidney relapse is needed to determine whether it is beneficial to tailor therapy based on biopsy findings.

12.9: Treatment of resistant disease

12.9.1: In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (*Not Graded*)

12.9.2: Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens (see Section 12.3). (*Not Graded*)

12.9.3: We suggest that nonresponders who have failed more than one of the recommended initial regimens (see Section 12.3) may be considered for treatment with rituximab, i.v. immunoglobulin, or CNIs. (*2D*)

RATIONALE

- Most patients are expected to show some evidence of response to treatment after a year of therapy, although complete remission may occur beyond a year.
- There are no prospective data on patients who fail to achieve at least partial response; it is reasonable, however, to repeat biopsy and determine if there has been a change in kidney pathology that could account for treatment failure.
- There are no prospective data on patients who fail initial therapy; however, it is reasonable to try a second course of initial therapy using an alternative regimen, as dictated by repeat biopsy.
- There have been small studies of "rescue" therapies for patients who have been refractory despite multiple treatment attempts.

In both prospective and retrospective LN cohorts, despite treatment with different protocols and follow-up under different definitions of remission, the majority of patients who remitted did so within 1 year of therapy.[604,605,615,618,645] Studies generally show that 50% of patients had a remission (complete or partial) by 12 months, with another 5–25% remitting by 24 months. Among complete remissions, about half were achieved by 12 months, and the other half by 20–24 months.

There is no consensus definition of refractory LN. A patient may be considered refractory if conventional cyclophosphamide regimens have been tried without success, and non-cyclophosphamide regimens have not worked. If repeat kidney biopsy confirms active LN is the cause of continuing clinical abnormalities, there is no definitive information to guide therapy. The following "salvage" treatments have only been evaluated in small observational studies.

The evidence that refractory LN can be treated with rituximab comes only from small, open-label studies.[623,688] Many of these patients had failed multiple attempts at treatment with the conventional therapies described previously. Rituximab may be considered as a "rescue therapy" when usual therapeutic options have been exhausted. This use of rituximab is in contrast to its lack of utility as add-on therapy to an initial standard regimen (Regimen D) for proliferative LN.[642]

The evidence for using i.v. immunoglobulin in refractory cases is of very low quality. It has been used in a handful of patients with proliferative LN, and in some has shown comparable efficacy to cyclophosphamide (reviewed by Rauova *et al.*[689] Some formulations of i.v. immunoglobulin (sucrose-containing) have shown nephrotoxicity, and are therefore best avoided in patients with pre-existing kidney impairment.

There is only evidence from small prospective, open-label trials for using low-dose cyclosporine (2.5 mg/kg/d) to treat refractory LN.[690,691] Although kidney function did not improve, most patients had a reduction in proteinuria, resolution of hematuria, and needed lower doses of corticosteroids. Similarly, a prospective trial used tacrolimus (3 mg/d) in patients with LN in whom corticosteroids could not be reduced, and demonstrated improvement in proteinuria and C3 levels.[692]

RESEARCH RECOMMENDATIONS

- A globally accepted definition of nonresponse needs to be developed.
- The salvage therapies discussed in the text must be subject to RCTs to determine effect on remission and kidney outcomes.

12.10: Systemic lupus and thrombotic microangiopathy

12.10.1: We suggest that the antiphospholipid antibody syndrome (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by anticoagulation (target international normalized ratio [INR] 2–3). (*2D*)

12.10.2: We suggest that patients with systemic lupus and thrombotic thrombocytopenic purpura (TTP) receive plasma exchange as for patients with TTP without systemic lupus. (*2D*)

BACKGROUND

Lupus-associated thrombotic microangiopathies (TMA) may occur alone or in combination with immune-complex LN. TMA in systemic lupus may occur in association with accelerated hypertension, systemic sclerosis, TTP, or in lupus anticoagulant/APS.

While TMA associated with APS, TTP, and accelerated hypertension is often characterized by AKI, APS can also cause slowly progressive kidney impairment with few specific clinical manifestations. In retrospective studies, kidney APS occurred in about 30% of systemic lupus patients.[693,694] Lupus anticoagulant was present in 30–52% of those with kidney APS, while 72–95% of patients had anticardiolipin antibodies, but 15% had neither of these serologic markers.[693,695] Routine testing does not identify all antiphospholipid antibodies; therefore, those with TMA who are antiphospholipid antibody–negative are treated in the same way as antibody-positive patients. A high index of suspicion is needed along with a kidney biopsy to confirm the diagnosis.

RATIONALE

- APS occurs frequently in systemic lupus, and there is moderate-quality evidence that failure to treat it may lead to CKD or ESRD, despite adequate control of LN or other systemic lupus manifestations with immunosuppression.
- Although there are no specific studies of anticoagulation for APS with systemic lupus, there have been two RCTs of the intensity of warfarin therapy in APS.[696,697] They provided moderate-quality evidence of no difference in thrombotic events if the INR was 2–3 or 3–4, but that bleeding complications were higher when INR was maintained greater than 3.
- TTP in lupus is associated with a high mortality.[698] There are no RCTs to guide treatment of TTP in the setting of systemic lupus, but it seems appropriate to use regimens beneficial in TTP without lupus.

RESEARCH RECOMMENDATIONS

- A clinical trial is needed to determine the effect of treating APS on long-term kidney function.
- A clinical trial is needed to determine the efficacy of plasma exchange in TTP, in the setting of systemic lupus.

12.11: Systemic lupus and pregnancy

12.11.1: We suggest that women be counseled to delay pregnancy until a complete remission of LN has been achieved. (*2D*)

12.11.2: We recommend that cyclophosphamide, MMF, ACE-I, and ARBs not be used during pregnancy. (*1A*)

12.11.3: We suggest that hydroxychloroquine be continued during pregnancy. (*2B*)

12.11.4: We recommend that LN patients who become pregnant while being treated with MMF be switched to azathioprine. (*1B*)

12.11.5: We recommend that, if LN patients relapse during pregnancy, they receive treatment

with corticosteroids and, depending on the severity of the relapse, azathioprine. (*1B*)

12.11.6: If pregnant patients are receiving corticosteroids or azathioprine, we suggest that these drugs not be tapered during pregnancy or for at least 3 months after delivery. (*2D*)

12.11.7: We suggest administration of low-dose aspirin during pregnancy to decrease the risk of fetal loss. (*2C*)

RATIONALE

- Data suggest that active LN or LN in partial remission is associated with an increase in fetal loss and an increased rate of kidney relapse during pregnancy.
- Cyclophosphamide, MMF, ACE-I, and ARBs are teratogenic.
- Hydroxychloroquine, azathioprine, and corticosteroids have been used safely during pregnancy in patients with systemic lupus; low-dose aspirin may decrease fetal loss in systemic lupus.

The risk of fetal loss in patients with LN has been examined in several retrospective series. In a nested case-control study of 78 pregnancies, the incidence of fetal loss was not different in patients with a history of LN compared to systemic lupus patients with no history of LN.[699] In patients with LN in remission, fetal loss of 8–13% has been documented.[700–702] However, in patients with active LN, fetal loss was significantly higher at 35%.[702] In addition to the clinical activity of LN, hypocomplementemia appears to be a risk factor for fetal loss, whereas the use of low-dose aspirin may be protective. In a retrospective study of 113 pregnancies in patients with systemic lupus and LN, hypocomplementemia conferred a RR of 19 for fetal loss, and aspirin conferred a RR of 0.11.[701] All the patients in this investigation were Caucasian, so the results may not be applicable to other ethnicities.

Hydroxychloroquine should be continued in pregnancy because its withdrawal may lead to flares of lupus, including LN.[703]

There may be additional risk to the kidneys of patients with LN who become pregnant. One study noted that kidney relapses and progressive kidney dysfunction were not different between pregnant and nonpregnant patients with LN.[699] In other studies, kidney relapses were more common in pregnancies occurring when only partial remission of LN had been achieved, or in patients who had more than 1 g/d proteinuria or kidney impairment.[700–702] Kidney relapse rates of 10–69% have been reported during or following pregnancy.[699–702]

12.12: LN in children

12.12.1: We suggest that children with LN receive the same therapies as adults with LN, with dosing based on patient size and GFR. (*2D*)

RATIONALE

- LN in children shows the same range of clinical and pathological phenotypes as is seen in adults.
- There are no RCTs of LN therapy in children.

Therefore, we suggest that children with LN be treated with the regimens recommended earlier in this chapter. The research recommendations made under 12.1–12.10 also apply to children.

SUPPLEMENTARY MATERIAL

Supplementary Table 71: Evidence profile of RCTs of MMF vs. Cyc for induction therapy in lupus nephritis.
Supplementary Table 72: Summary table of RCTs examining MMF vs. IV Cyc for induction therapy in patients with lupus nephritis (categorical outcomes).
Supplementary Table 73: Summary table of RCTs examining MMF vs. IV Cyc for induction therapy in patients with lupus nephritis (continuous outcomes).
Supplementary Table 74: Existing systematic review on Cyc vs. AZA for induction treatment in patients with lupus nephritis.
Supplementary Table 75: Summary table of RCT examining Cyc vs. AZA for induction treatment in patients with lupus nephritis (categorical outcomes).
Supplementary Table 76: Summary table of RCT examining Cyc vs.AZA for induction treatment in patients with lupus nephritis (continuous outcomes).
Supplementary Table 77: Summary table of RCT examining low vs. high dose IV Cyc in patients with lupus nephritis (categorical outcomes).
Supplementary Table 78: Existing systematic review on IV vs. p.o. Cyc treatment in patients with lupus nephritis.
Supplementary Table 79: Summary table of RCT examining IV Cyc vs. p.o. Cyc in patients with lupus nephritis (categorical outcomes).
Supplementary Table 80: Summary table of RCT examining Cyc vs. AZA for maintenance therapy in patients with lupus nephritis (categorical outcomes).
Supplementary Table 81: Summary table of RCT examining Cyc vs. AZA for maintenance therapy in patients with lupus nephritis (continuous outcomes).
Supplementary Table 82: Summary table of RCT examining IV Cyc vs. prednisone in patients with membranous lupus nephritis (categorical outcomes).

Supplementary Table 83: Summary table of RCT examining IV CsA vs. prednisone in patients with membranous lupus nephritis (categorical outcomes).
Supplementary Table 84: Summary table of RCT CsA vs. IV Cyc in patients with membranous lupus nephritis (categorical outcomes).
Supplementary Table 85: Summary table of RCT examining rituximab + Cyc vs. rituximab in patients with proliferative lupus nephritis (categorical outcomes).
Supplementary Table 86: Summary table of RCT examining rituximab + Cyc vs. rituximab in patients with proliferative lupus nephritis (continuous outcomes).
Supplementary Table 87: Summary table of RCT examining TAC vs. placebo in patients with lupus nephritis (categorical outcomes).
Supplementary Table 88: Summary table of RCT examining TAC vs. placebo in patients with lupus nephritis (continuous outcomes).
Supplementary Table 89: Summary table of a study examining TAC vs. standard protocols of steroid + p.o. Cyc or AZA in patients with class V lupus (categorical outcomes).
Supplementary Table 90: Summary table of a study examining TAC vs. standard protocols of steroid + p.o. Cyc or AZA in patients with class V lupus (continuous outcomes).
Supplementary Table 91: Summary table of a study examining AZA vs. IV Cyc maintenance therapy in patients with lupus nephritis (categorical outcomes).
Supplementary Table 92: Summary table of a study examining MMF vs. IV Cyc maintenance therapy in patients with lupus nephritis (categorical outcomes).
Supplementary Table 93: Evidence profile of studies examining MMF vs. AAZA maintenance therapy in patients with lupus nephritis.
Supplementary Table 94: Summary table of studies examining MMF vs. AZA maintenance therapy in patients with lupus nephritis (categorical outcomes).
Supplementary Table 95: Summary table of studies examining MMF vs. AZA maintenance therapy in patients with lupus nephritis (continuous outcomes).
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php