Lupus nephritis management guidelines compared

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ABSTRACT

In the past years, many (randomized) trials have been performed comparing the treatment strategies for lupus nephritis. In 2012, these data were incorporated in six different guidelines for treating lupus nephritis. These guidelines are European, American and internationally based, with one separate guideline for children. They offer information on different aspects of the management of lupus nephritis including induction and maintenance treatment of the different histological classes, adjunctive treatment, monitoring of the patient, definitions of response and relapse, indications for (repeat) renal biopsy, and additional challenges such as the presence of vascular complications, the pregnant SLE patient, treatment in children and adolescents, and considerations about end-stage renal disease and transplantation. In this review, we summarize the guidelines, determine the common ground between them, highlight the differences and discuss recent literature.

Keywords: guideline, lupus nephritis, management, systemic lupus erythematosus, treatment

INTRODUCTION

Lupus nephritis (LN) is associated with poor survival [1, 2] and considerable morbidity, particularly for patients who develop end-stage renal disease (ESRD) and require renal replacement therapy. The development of renal involvement within the course of disease ranges from ~20 to 60% of systemic lupus erythematosus (SLE) patients [3] with the highest risk of renal disease and renal failure in young black women [4, 5]. Therapeutic possibilities have expanded from the solitary use of corticosteroids to the addition of a wide range of immunosuppressive drugs and other supportive treatment. Many trials have been conducted in the past 40 years leading to the publication of six guidelines in 2012 on the management of LN (Table 1) [6–11]. These guidelines are American and European based, with separate guidelines from Spain and the Netherlands, with the addition of the KDIGO (Kidney Disease Improving Global Outcomes) guideline that is considered to be international. All guidelines were developed on the basis of extensive literature searches and (consensus) meetings. Furthermore, each guideline indicated the level of evidence or strength of a statement/recommendation, or both, for all topics (Supplementary data, Table S3). All guidelines were published in the same year and based on the same body of evidence, and their main statements are congruent. However, there are also notable differences between them. The aim of this review is to compare the recent guidelines, outline a common view and highlight the differences, in particular in relation to indications for (repeat) renal biopsy, induction and maintenance treatment of the different classes, adjunctive treatment, monitoring of the patient, definitions of response and relapse, and additional circumstances such as the presence of vascular complications, the pregnant SLE patient, treatment in children and adolescents, and considerations about ESRD and transplantation (Tables 2 and 3, Supplementary data, Table S1 and S2). We will also...
discuss recent literature and how to proceed further to increase the level of evidence-based patient care.

**RENAI L BIOPSY**

All guidelines recommend a renal biopsy when there is a suspicion of renal involvement, because clinical and laboratory parameters cannot accurately predict the histological class. Early diagnosis and treatment have been shown to improve outcomes [13, 14]. The criteria for suspicion of renal involvement, however, differ. The common view is that an unexplained decrease in renal function and proteinuria are indications for a renal biopsy. Also, an active urine sediment raises the level of suspicion of renal involvement and may be an additional argument for a renal biopsy. The GEAS (Spanish Society of Internal Medicine and Spanish Society of Nephrology) considers an active urine sediment alone a sufficient cause for biopsy. The required levels of proteinuria differ between the guidelines, but most use a urine protein–creatinine ratio of 50 mg/mmol (equivalent to ~0.5 g/24 h) as a cut-off.

The biopsy is classified according to the system proposed by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) in 2003 [15]. A minimum of 10 glomeruli is required to reasonably exclude focal disease, and the biopsy should be examined by light microscopy, immunofluorescence and if possible, electron microscopy. Furthermore, data on activity and chronicity should be quantified (though activity and chronicity indices are not obligatory), and vascular and interstitial lesions described. The histological class plays a fundamental role in the ensuing therapeutic decision process.

Although the evidence is sparse, in cases of worsening of disease, disease refractory to treatment or relapse, a repeat biopsy can be considered to determine activity and chronicity or detect other pathologies. Some also suggest taking a biopsy at the end of induction treatment to determine the histological response, as clinical parameters may underestimate (histological) response [16, 17]. However, this strategy has not been officially tested in a controlled study, but repeat renal biopsy has been shown to have prognostic value [18–21].

**TREATMENT CLASS II**

There is little agreement among the guidelines on treatment of Class II LN due to lack of evidence. Proteinuria should primarily be managed with renin–angiotensin–aldosterone system (RAAS) inhibitors. The role of immunosuppression, however, is less clear. The ACR (American College of Rheumatology) guideline states that Class II LN generally does not require immunosuppressive treatment. The EULAR/ERA-EDTA (European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association), however, recommends low to moderate doses of oral glucocorticoids (0.25–0.5 mg/kg/day) alone or in combination with azathioprine (AZA, 1–2 mg/kg/day), if necessary as a steroid-sparing agent, in cases of proteinuria over 1 g/24 h, especially in the presence of glomerular haematuria. In the GEAS guideline, steroids up to 0.5 mg/kg/day, if necessary with AZA or mycophenolate mofetil (MMF), for 6–12 months are suggested for Class II nephritis with proteinuria (>1–2 g/24 h) and/or a deteriorated renal function that are not attributable to functional factors. The suggestions in the KDIGO guideline for the use of immunosuppressive therapy focus on the presence/coexistence of podocytopathy [i.e. minimal change disease (MCD)] in a subset of patients with Class II LN [22, 23], and KDIGO suggests treating such patients with nephrotic-range proteinuria (>3 g/24 h) with corticosteroids or calcineurin inhibitors (CNIs) as for MCD, but this presentation was not discussed in the ACR guidelines.

**INDUCTION AND MAINTENANCE TREATMENT CLASS III/IV**

Over the past decade, several randomized controlled trials (RCTs) have been conducted for Class III and IV LN, both in
### Table 2. Guidelines compared: common views and differences

<table>
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<th>Common view</th>
<th>Differences</th>
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| Indication for renal biopsy | **Proteinuria:**  
  - Most: isolated proteinuria ≥0.5 g/24 h  
  - ACR: isolated proteinuria ≥1.0 g/24 h or ≥0.5 g/24 h and haematuria (5 RBCs/HPF) or cellular casts  
  Active sediment: sufficient to warrant biopsy in GEAS, others consider a biopsy, sometimes when in combination with low levels of proteinuria |
| Reproducible proteinuria (required levels: different) |  |
| Active sediment raises level of suspicion for LN and may be an additional argument for a renal biopsy |  |
| Biopsy evaluation | According to ISN/RPS 2003 classification system for LN  
  Examine by light microscopy, immunofluorescence and if possible electron microscopy |
| Indication for repeat biopsy |  |
| Quantify data on activity and chronicity and describe vascular and interstitial lesions |  |
| Consider in case of:  
  - Worsening of disease or disease refractory to treatment  
  - Relapse, to demonstrate change or progression in histological class, change in activity and chronicity (index) or other pathologies |  |
| Treatment Class II | Treat proteinuria with RAAS (first)  
  - Indication for repeat biopsy  
  - Consider in case of:  
    - Worsening of disease or disease refractory to treatment  
    - Relapse, to demonstrate change or progression in histological class, change in activity and chronicity (index) or other pathologies |
| Oral glucocorticoids with or without three iv pulses methylprednisolone (MP) at start induction + ivCYC or MMF |  |
| Induction treatment Class III/IV without crescents (and/or other adverse parameters) |  |
| ACR: no immunosuppressive treatment  
  EULAR/ERA-EDTA: proteinuria >1 g/24 h, especially in the presence of glomerular haematuria; low to moderate doses oral glucocorticoids (0.25–0.5 mg/kg/day) alone or in combination with AZA (1–2 mg/kg/day), if necessary  
  KDIGO: proteinuria <1 g/24 h: treat as dictated by extrarenal manifestations. Proteinuria >3 g/24 h: corticosteroids or CNI as described for MCD  
  GEAS: significant proteinuria (>1–2 g/24 h) and/or deteriorated renal function that is not attributable to functional factors; steroids up to 0.5 mg/kg/day, possibly plus AZA or MMF for 6–12 months  
  Dosage and preferences for different severities (see also next section) and ethnic groups:  
  - Glucocorticoids:  
    - MP dose ranging from 250 to 1000 mg/day (or weight dependent in children)  
    - MP not always recommended; dependent on combination with MMF or ivCYC, or on severity  
    - Oral dose ranging from 0.5 to 1 mg/kg/day, sometimes depending on combination with MP, MMF or ivCYC  
    - Tapering schedule: unclear  
  - MMF:  
    - Ranging from 2 to 3 g total daily dose  
    - Sometimes preferred over ivCYC in patients of African or Hispanic descent  
  - ivCYC:  
    - Either high dose (NIH: 0.5–1 g/m² monthly for 6 months) or low dose (Eurolupus: 500 mg fortnightly for 3 months); low dose usually preserved for (European) Caucasians and sometimes only for relatively mild disease  
    - In case of low-dose ivCYC, combine pulses MP |
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<td><strong>Common view</strong></td>
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<td><strong>Induction treatment Class IV or IV/V with crescents (and/or other adverse parameters)</strong></td>
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<td><strong>Treatment for refractory disease</strong></td>
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Pregnancy

Continue HCQ

Allowed: glucocorticoids (non-fluorinated), AZA, CNIs, methyldopa, labetalol or nifedipine

Not allowed: MMF, ivCYC, RAAS inhibitor

Consider low-dose acetylsalicylic acid to reduce risk of pre-eclampsia and fetal loss

Monitor closely, preferably by a multidisciplinary team

Do not taper glucocorticoids or AZA during pregnancy or within 3 months thereafter (KDIGO)

Plan pregnancy when:

- EULAR/ERA-EDTA: stable (uPCR <50 mg/mmol, GFR preferably over 50 mL/min) for 6 months
- GEAS: (partial) remission for 6 months
- KDIGO: preferably delay until complete remission
- ACR: not specified

Vascular complications

No consensus

EULAR/ERA-EDTA: ASPN; consider HCQ and/or antiplatelet/anticoagulant treatment. In case of definite APS, start anticoagulant treatment

ACR: treat TMA with plasma exchange therapy

KDIGO/GEAS: ASPN; anticoagulant treatment (INR 2–3)

KDIGO: treatment for TTP is plasma exchange as in patients without lupus

Monitoring

Determine at each visit: body weight, BP, sCr, proteinuria, urinary sediment, C3/C4, anti-dsDNA (and serum albumin and complete blood count)

Schedule visits:

- Active nephritis: approximately monthly, or more frequently
- No active nephritis: every 3–6 months

Management of ESRD

Renal replacement therapy:

- Increased risk of infection in patients still on immunosuppressives (EULAR/ERA-EDTA)

- Increased risk of vascular access thrombosis in patients with aPL (EULAR/ERA-EDTA)

- If lupus is inactive offer peritoneal dialysis; if lupus is active offer haemodialysis (GEAS)

Transplantation:

- If lupus activity absent or low for 3–6 (EULAR/ERA-EDTA) or 6–12 (GEAS) months

uPCR 100 mg/mmol ≡ 1000 mg/g ≡ 1 g/24 h [12]. ACR, American College of Rheumatology; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; APSN, antiphospholipid-associated nephropathy; AZA, azathioprine; BP, blood pressure; CARRA, Childhood Arthritis and Rheumatology Research Alliance; CNI, calcineurin inhibitor; anti-dsDNA, antibodies to double-stranded DNA; DWP, Dutch Working Party on Systemic Lupus Erythematosus; ESRD, end-stage renal disease; EULAR/ERA-EDTA, European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association; GEAS, Systemic auto-immune disease group of the Spanish Society of Internal Medicine and Spanish Society of Nephrology; GFR, glomerular filtration rate; HCQ, hydroxychloroquine; HPF, high-power field; ISN/RPS, International Society of Nephrology/Renal Pathology Society; ivCYC, intravenous cyclophosphamide; KDIGO, Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group; LN, lupus nephritis; MCD, minimal change disease; MMF, mycophenolate mofetil; MP, methylprednisolone; NIH, National Institute of Health; RAAS, renin–angiotensin–aldosterone system; RBC, red blood cell; sCr, serum creatinine; uPCR, urine protein–creatinine ratio.
the induction and in the maintenance phase. Consequently, the guidelines are uniform in their recommendations for induction treatment: intravenous cyclophosphamide (ivCYC) or MMF (2–3 g total daily dose) in combination with oral glucocorticoids with or without three pulses of intravenous methylprednisolone (MP) at start of induction treatment. Although, in general, the use of both oral and intravenous glucocorticoids has been proven effective, evidence is scarcer concerning dose and duration and recommendations are mainly based on expert opinion. In the guidelines, the initial dose of oral glucocorticoids varies from 0.5 to 1.0 mg/kg/day. Only one small RCT compared high- (1 mg/kg) and low (0.5 mg/kg)-dose oral glucocorticoids (in a background of enteric-coated mycophenolic acid). This study demonstrated an equal percentage (~20%) of complete responses at 24 weeks, although non-inferiority was not proven. It did, however, show a decrease in infections in favour of the low-dose group [24]. Furthermore, advice for tapering of glucocorticoids is usually fairly general, except for the guideline from the Dutch Working Party on SLE (DWP), which devised a schedule for tapering (Supplementary data, Table S1). The use of pulse MP at induction is not always recommended and is reserved by some of the guidelines for more severe cases. However, there is some indication that the use of pulse MP combined with medium-dose oral glucocorticoids may be as effective as high-dose oral glucocorticoids in inducing remission, but with less toxicity [25]. MMF and ivCYC have similar efficacy and adverse event rates when used with glucocorticoids for remission induction, but MMF avoids adverse effects on fertility. For ivCYC, both the low-dose Eurolupus regimen (500 mg fortnightly for 3 months) and the higher dose NIH regimen (0.5–1 g/m² monthly for 6 months) can be used. However, the low dose is usually preferred for (European) Caucasians and sometimes only for milder cases, because the original trials were mostly in this group of patients [26, 27]. The ACCESS trial, communicated after publication of the guidelines, showed no benefit of abatacept as add-on to induction therapy. However, in a predominantly non-Caucasian study population, comparable response rates to low-dose ivCYC were observed to those previously reported, suggesting that low-dose ivCYC may be as effective in non-Caucasians as in Caucasians [28], although further evidence will be required. Finally, MMF is sometimes preferred over ivCYC in patients from African or Hispanic descent, based on a ‘post-hoc’ subgroup analysis of the ALMS trial [29]. Some of the guidelines advise more aggressive therapy in patients with crescents in the biopsy specimen, as detailed in Table 2. The EULAR/ERA-EDTA and KDIGO guidelines also state that patients should have active lesions (Class III/IV<sub>A</sub> or Class III/IV<sub>AC</sub>) to be treated and should not have merely chronic lesions (Class III/IV<sub>C</sub>).
For severe LN, although not adequately defined, there is less evidence as these patients are often excluded from RCTs. However, a subgroup analysis of the ALMS trial in patients with a baseline estimated glomerular filtration rate <30 mL/min did not reveal a difference between ivCYC and MMF [30]. Unfortunately, numbers were small (32 in total), and there was no follow-up beyond the induction phase. Recently, Rovin et al. performed a systematic review using results extracted from clinical trials and drawn from expert opinion. Severe LN was arbitrarily defined by renal histology, resistance to therapy or GFR at presentation. They showed that ivCYC and MMF are equally effective in inducing remission. For long-term follow-up (5 years), however, results from retrospective and observational studies suggest there may be a better preservation of renal function and fewer relapses with ivCYC [31]. Long-term follow-up data from RCTs, however, are lacking.

In the maintenance phase of treatment, MMF (1–2 g/day) or AZA (1.5–2.5 mg/kg/day) is recommended by all guidelines, supported by low-dose oral glucocorticoids. The EULAR/ERA-EDTA recommends MMF over AZA if there was a response to MMF at induction based on the combined results from the ALMS [32] and MAINTAIN trials [33]. The GEAS advises MMF over AZA, based on the results from the ALMS trial, although data on long-term effects of MMF are still lacking. Also, a recent meta-analysis of four trials (including MAINTAIN and ALMS) showed that there is no difference between MMF and AZA with respect to preventing relapse, progression to end-stage renal failure, death and doubling of serum creatinine [34]. Finally, with respect to duration of treatment, the guidelines differ: at least 3 years (EULAR/ERA-EDTA) or at least 1 (KDIGO) or 2 (GEAS) years after (complete) remission. Due to the length of completed studies, there is no advice on the optimal duration of therapy beyond 3 years.

**MONITORING**

The guidelines differ in their approach but agree that patients with active nephritis should have a visit scheduled at least every month, particularly at induction, relapse and withdrawal of treatment. If there is no active nephritis every 3–6 months should suffice, although vigilance is required for prompt identification of disease relapse. At each visit, body weight, blood pressure, serum creatinine (sCr), proteinuria, urinary sediment, complement levels, anti-dsDNA titre and according to some serum albumin and complete blood count should be determined. The ACR states that some of the aforementioned can be determined at larger intervals than others (blood pressure and urinalysis frequent; anti-dsDNA less frequent) and drafted a separate monitoring schedule for pregnancy (Table 2 and Supplementary data, Table S1). Recommendations in this area are all based on expert opinion. Nevertheless, they can still serve as a guideline for the practicing physician. Also, a recommendation from the EULAR for monitoring patients with SLE was previously published [40].

**ADJUNCTIVE TREATMENT/TREATMENT FOR COMORBIDITIES**

All guidelines recommend blood pressure control (target <130/80 mmHg), treatment of hyperlipidaemia with statins (target LDL <100 mg/dL or 2.6 mmol/L) and treatment of proteinuria with RAAS inhibition. The guidelines agree that all SLE patients should have a background of hydroxychloroquine (HCQ) unless contraindicated, since this is associated with less damage accrual [41]. There is a paucity of randomized evidence for the efficacy of HCQ on nephritis with only two retrospective studies supporting its use [42,43]. Patients receiving HCQ have a risk of developing retinopathy and should therefore be screened by the ophthalmologist at baseline and yearly after 5 years. Patients with severe renal or hepatic disease are at higher risk for developing retinopathy, due to less clearance of the drug. In those patients, reducing the dose should be considered to avoid toxicity. Other recommendations made by one or more of the guidelines are listed in Table 2 and involve treatment for side effects of drugs, prevention of clotting events and...
DEFINITIONS OF RESPONSE AND RELAPSE

When communicating about patients, either in trials or in clinical practice, it is essential that definitions for disease parameters such as partial and complete response and relapse or flare are the same. Previously, a very stringent European consensus statement was published on the terminology used in the management of lupus nephritis [44]. However, the choice of primary end point in clinical trials can also substantially influence the ability to detect therapeutic benefit, as demonstrated by Wofsy et al. [45]. The common ground and differences for the definitions of complete and partial response, relapse or flare, and refractory disease are outlined in Table 3 and Supplementary data, Table S2.

TREATMENT FOR REFRACTORY DISEASE

Although the definition for refractory disease is stated differently by the various guidelines, there agreement on the treatment, despite the lack of clinical trial evidence for these approaches. It is generally advised to switch from MMF to ivCYC or vice versa if induction treatment fails. Some guidelines also state that again three pulses of intravenous MP should be administered. If this approach fails, the guidelines recommend other options: rituximab, as add-on or monotherapy, CNIs (also as add-on or monotherapy) or intravenous immunoglobulins. Of these, the main focus in literature has been on the use of rituximab. However, with the LUNAR trial of rituximab as add-on to a steroid-MMF combination failing to meet its endpoint, it has not yet been proven effective in an RCT. Putative explanations for this failure include the possible overtreatment of relatively mild disease, short follow-up and underpowered study for the detection of an effect mainly consisting of partial responses [46]. Recently, a summary of the literature on the use of rituximab in refractory LN was published [47], which suggests that rituximab can induce a response in patients who did not achieve remission on standard therapy. Also, Jónsdóttir and colleagues [48] recently showed in a group of 25 patients that add-on of rituximab to ivCYC and glucocorticoids resulted in both clinical and histological improvements in the majority of patients. A recent, non-randomized, prospective study found promising results for a steroid-sparing induction regimen [49] consisting of two doses of rituximab (1 g) and MP (500 mg) on Day 1 and 15, and maintenance with MMF without oral steroids. A Phase 3 open-label multicentre investigator-led RCT (RITUXILUP, NCT01773616) will start in 2015 comparing this regimen with a 'standard' oral glucocorticoid/MMF regimen.

Although RCTs are lacking, there is a growing body of evidence that CNIs may be useful in refractory disease, but one should be aware of the nephrotoxic effects, especially in patients with decreased renal function. These nephrotoxic effects (reviewed by Naesens et al. [50]) seem to be less for tacrolimus than for ciclosporin. Although not studied in refractory disease, in a recent Chinese randomized trial, the combination of MMF (1.0 g/day) with tacrolimus (4 mg/day) was proven superior to ivCYC (0.5–1 g/m² every 4 weeks for six doses) in achieving complete remission in patients with Class IV, Class V and Class IV + V LN [51]. This could be due to a faster anti-proteinuric effect of tacrolimus, and longer follow-up data are needed to determine the comparable efficacy of the two regimens.

PREGNANCY

Pregnancy should not be planned until remission is reached and maintained for 6 months (EULAR/ERA-EDTA and GEAS). HCQ should be continued as multiple studies (reviewed by Ruiz-Irastorza et al. [41]) have demonstrated its safety in pregnancy. RAAS inhibitors, MMF and cyclophosphamide are prohibited during pregnancy. As alternatives, AZA, CNIs, methylprednisolone, labetolol or nifedipine can be prescribed, despite the classification of AZA (the same as MMF and ivCYC) as Category D by the Food and Drug Administration (positive evidence of human fetal risk based on adverse reaction data, potential benefits may warrant use of the drug in pregnant women despite the potential risk). AZA is considered safe during pregnancy as there is no evidence that AZA increases the risk of congenital abnormalities (in contrast to MMF and CYC) and AZA cannot be metabolized to the active metabolite 6-mercaptopurine by the fetal liver [52, 53]. Low-dose oral glucocorticoids (non-fluorinated) are acceptable. It is advised by the KDIGO not to taper glucocorticoids or AZA during pregnancy or for 3 months thereafter. Furthermore, low-dose acetylsalicylic acid should be considered to reduce the risk of pre-eclampsia. Finally, all patients should be monitored closely, preferably by a multidisciplinary team that is used to managing such patients and is aware of the need to distinguish between a flare and pre-eclampsia, which may also coexist.

VASCULAR COMPLICATIONS

Antiphospholipid syndrome-associated nephropathy (APSN) is a vascular nephropathy that can occur in SLE patients and may be associated with the presence of antiphospholipid (aPL) antibodies. The EULAR/ERA-EDTA guideline takes the use of HCQ and/or antiplatelet or anticoagulant treatment into consideration, while the KDIGO and GEAS merely suggest treatment with anticoagulants (INR 2–3). The ACR suggests treating thrombotic microangiopathy (TMA) primarily with plasma exchange. This area is further complicated by the inconsistent terminology used. TMA is a histological lesion, which is part of the APSN spectrum, but also has a clinical counterpart with systemic manifestations such as the presence of schistocytes in peripheral blood. Thrombotic thrombocytopenia purpura (TTP) is a clinical syndrome associated with TMA in the renal biopsy, recommended to be treated promptly with plasma exchange by KDIGO (and other guidelines for idiopathic TTP, as TTP especially in SLE has a high mortality). In summary,
recommendations differ because of inconsistent terminology and lack of evidence. Until this is solved, we recommend viewing TMA in the renal biopsy in the clinical context when determining treatment. If APSN is considered to be a small vessel manifestation of APS and laboratory criteria for the diagnosis of APS are met, it may be wise to treat it as such (with antplatelet or anticoagulation therapy), at least until new evidence becomes available.

**MANAGEMENT OF ESRD AND TRANSPLANTATION**

The modality of dialysis should be determined by patient choice. However, the risk of infection is increased with the use of immunosuppressive drugs. Hence, the GEAS suggests peritoneal dialysis should only be offered to patients with inactive disease on minimal immunosuppression. Haemodialysis is suitable for patients with active disease/more immune suppression.

It is advised to determine the presence of aPL antibodies, because this can increase the risk of vascular access thrombosis during dialysis and vascular events in the transplant. Lupus activity should be absent or low for a period of 3–6 months (EULAR/ERA-EDTA) or 6–12 months (GEAS) to be eligible for transplantation. Although ESRD is often associated with remission of lupus activity, this is not universal and extrarenal lupus flares can still occur; patients should be managed accordingly.

**CHILDREN AND ADOLESCENTS**

The rate of developing LN during the course of disease is higher in children than in adults [54]. However, large trials comparing different treatment strategies in juvenile LN are lacking. The guidelines generally advise the same treatment strategies as for adults, except for the CARRA consensus treatment plan, which is specifically aimed at children and adolescents. For dosages of the immunosuppressive drugs in children, we refer to this treatment plan. In 2012, the first results from an RCT, a subgroup analysis of the ALMS trial, were published [55]. This subgroup analysis included adolescents aged 12–18 years. Although the numbers were small (24 patients in the induction phase and 16 in the maintenance phase) and therefore not sufficient to yield statistically significant results, it was noted that in general there was similar efficacy in adolescents and adults. Due to the small numbers, the effect of ethnicity could not be determined.

**CONCLUSION**

Although a substantial part of the management of LN is evidence based, a significant part still rests on uncontrolled trials and expert opinion. Despite an increase in clinical trial activity during the last decade, there are areas where evidence is lacking, such as for the treatment of severe and refractory LN and of children. Furthermore, although the most important outcome is the long-term follow-up beyond 10 years due to the risk of end-stage renal failure at this time despite initial improvement in disease parameters, these data are scarce. Finally, it must be kept in mind that all guidelines are meant to assist physicians in the management of LN, but they can never replace the insight of the experienced clinician in reaching a therapeutic strategy tailored to the individual patient.

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**SUPPLEMENTARY DATA**

Supplementary data are available online at http://ndt.oxfordjournals.org.

**CONFLICT OF INTEREST STATEMENT**

I.M.B. is a consultant for Roche; L.L.: Roche are providing drugs free of charge for the Rituxilup trial; honoraria/advisory boards/lecturing—GSK, Anthera Pharmaceuticals, MedImmune, Merck, Aspreva/Vifor Pharma, Biogen-Idec, UCB; C.G. is a consultant on clinical trial design and has received honoraria for consultancy, participation in scientific advisory boards and lecturing for UCB, GSK and Bristol-Myers Squibb, and has received honoraria from Aspreva/Vifor Pharma, MedImmune, Genentech, Roche and Merck Serono. D.J.: Roche/Genentech is providing drugs for the RITAZAREM trial; honoraria/advisory boards/lecturing—GSK, MedImmune, Merck, Biogen-Idec and UCB; V.T.: Lecturing for GSK and Roche.

**REFERENCES**


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