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SPECIAL ARTICLE

Dutch guidelines for diagnosis and therapy of proliferative lupus nephritis

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ABSTRACT

Proliferative lupus nephritis is a strong predictor of morbidity and mortality in patients with systemic lupus erythematosus. Despite improvements in the management of lupus nephritis, a significant number of the patients do not respond to immunosuppressive therapy and progress to end-stage renal failure. In order to optimise the diagnostic strategy and treatment of patients with proliferative lupus nephritis, guidelines are needed.

In this review, the Dutch Working Party on Systemic Lupus Erythematosus provides recommendations regarding four important areas in patients with proliferative lupus nephritis: I) indications for a first renal biopsy, II) definitions of treatment response, III) selection of treatment options, and IV) indications for a repeat biopsy.

KEYWORDS

Azathioprine, cyclophosphamide, mycophenolate mofetil, proliferative lupus nephritis

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterised by the production of auto-antibodies most prominent against nuclear antigens. Antibodies against nucleosomes and double-stranded DNA have a central role in the pathogenesis of the disease.[1] The systemic character of SLE is illustrated by the fact that all kinds of tissues and/or organs may be involved in this disease.[2]

In Europe, the incidence of SLE is estimated at 3.3 to 5.0 per 100,000 persons and the prevalence at 25.4 to 91.0 per 100,000 persons.[3] Most patients are women of childbearing potential. Lupus nephritis (LN) occurs in up to 50 to 75% of SLE patients during the course of the disease.[4,5] The incidence of kidney involvement differs with ethnicity: a higher incidence of LN has been reported among Black, Hispanic and Asian patients compared with Caucasian patients.[3,6] Although the clinical presentation may vary among patients, proliferative LN is a major cause of morbidity and mortality.[7,8] Progression into end-stage renal disease (ESRD) despite aggressive immunosuppressive therapy does occur.[9-11]

To date, no guidelines on how to manage patients with proliferative LN (ISN/RPS class III and IV) are available in the Netherlands although European guidelines have been published[12], and international (KDIGO) and US (American College of Rheumatology) guidelines are currently being developed. The Dutch Working Party on SLE has addressed this issue and developed recommendations based on opinions from expert panel meetings with nephrologists, rheumatologists and clinical immunologists, and a critical review of the present literature. A systemic search of the PubMed database was performed (1975 to January 2012), and all English language publications were considered. The following search terms were used: SLE, (refractory) LN, azathioprine, cyclophosphamide,

prednisone, mycophenolate mofetil (MMF), rituximab, hydroxychloroquine, renal biopsy, repeat biopsy, antiphospholipid syndrome nephropathy, induction treatment, maintenance treatment, and response.

The strength of evidence was graded using the following classification: Level A evidence represents data derived from multiple randomised controlled trials (RCT) or a meta-analysis; Level B from a single RCT or a non-randomised study; Level C from expert opinion.

In this article, we present recommendations regarding four important areas in the care of patients with proliferative LN: I) indications for a first renal biopsy, II) definitions of treatment response, III) selection of treatment options, and IV) indications for a repeat biopsy.

Table 1. *Abbreviated International Society of Nephrology/ Renal Pathology Society (ISN/RPS) classification of lupus nephritis 2003*[13]

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal proliferative lupus nephritis (involving <50% of all glomeruli)
Class IV	Diffuse proliferative lupus nephritis[a,b] (involving ≥50% of all glomeruli) *Segmental lesions:* IV-S (involving <50% of the glomerular tuft) *Global lesions:* IV-G (involving ≥50% of the glomerular tuft)
Class V	Membranous lupus nephritis[c]
Class VI	Advanced sclerosing lupus nephritis without active lesions

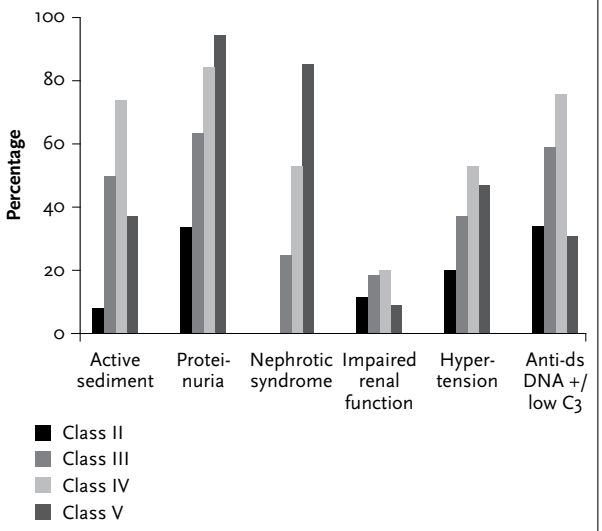
[a]Indicates the presence of active (A), active and chronic (A/C) and chronic (C) lesions; [b]Indicates the proportion of glomeruli with fibrinoid necrosis and cellular crescents; [c]Class V may occur in combination with class III or IV, in which case both will be diagnosed.

INDICATIONS FOR A FIRST RENAL BIOPSY IN PATIENTS WITH SLE

The occurrence of LN should be considered in any SLE patient with a recent onset of impaired kidney function, proteinuria and/or microscopic haematuria (≥5 red cells per high-power field). However, as these clinical features do not permit a reliable prediction of the class of LN (*figure 1*), the diagnosis must be confirmed by kidney biopsy, since this can have clinical consequences on treatment decisions.[2] Six classes of LN are distinguished in the current classification of the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) (*table 1*).[13] These histological findings provide the basis for treatment recommendations. Based on panel discussions, the Dutch Working Party formulated guidelines (as stated in *figure 2)* on when to perform a first renal biopsy in patients with SLE.

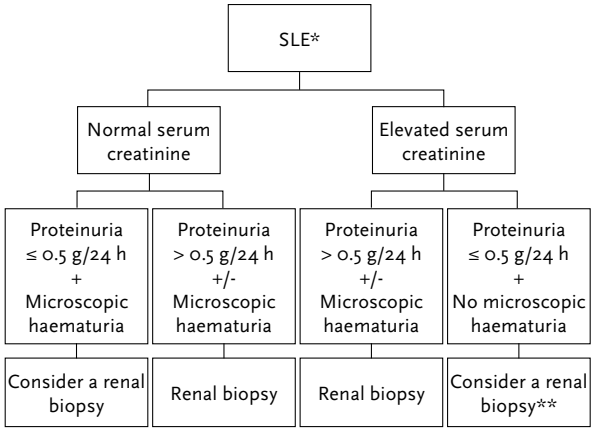
Although clinically silent proliferative LN occurs in a substantial proportion of patients, it is generally accepted to decide not to perform a renal biopsy in SLE patients who have a normal renal function, no haematuria and <0.5 g/24 hours of proteinuria (Level C).[14] In such patients renal parameters should be monitored carefully. In SLE patients presenting with >0.5 g/24 hours of proteinuria, after exclusion of other causes a renal biopsy is indicated, independent of the presence of microscopic haematuria

Figure 1. *Incidence of clinical symptoms in various forms of lupus nephritis*[19]



Lupus nephritis, based on the 1995 classification published under the auspices of the World Health Organization.[80]

Figure 2. *Indications to perform a first renal biopsy in patients with systemic lupus erythematosus*



***Systemic lupus erythematosus: at least 4 ACR criteria positive; **Consider a renal biopsy when either i) a persistent elevation of serum creatinine >30%, ii) other causes of renal impairment are excluded, iii) positive anti-phospholipid antibodies, iv) extra-renal involvement/presence of anti-dsDNA antibodies/ hypocomplementaemia.**

and/or an increase in serum creatinine (Level C). These patients may have focal or diffuse proliferative glomerulonephritis, or membranous lupus.

In SLE patients with microscopic haematuria in the absence of an increase in serum creatinine or proteinuria it is not clear whether a renal biopsy should be performed. Although prompt diagnosis after the onset of LN and subsequent initiation of appropriate therapy are associated with improved outcomes, persistent isolated microscopic haematuria has not been associated with a negative outcome so far and warrants close monitoring of other renal parameters (Level C).[15,16]

An increase in serum creatinine may implicate a proliferative LN. However, is it possible that these patients present without microscopic haematuria or proteinuria? Since clinical features do not permit a reliable prediction of the class of LN, the Dutch Working Party came to an opinion-based agreement that in this setting a biopsy should be considered when the observed increase in serum creatinine is persistent over several weeks and is >30%, together with the presence of either I) extra-renal lupus manifestations and/or serological activity and/or II) the presence of anti-phospholipid antibodies.[17-20] Moreover, in the absence of an obvious extra-renal explanation for deteriorating renal function a kidney biopsy may be warranted to exclude renal pathology other than LN, including a tubulo-interstitial nephritis, vascular disease (e.g. thrombotic microangiopathy or vasculitis), diabetes or drug-induced nephrotoxicity (Level C).

DEFINITIONS OF TREATMENT RESPONSE IN LN

Standard definitions of treatment response have been assessed in proliferative LN.[21-23] However, no single initial renal parameter has been validated as a marker for determining response.[12,23] Nonetheless, changes in renal function have been associated with renal outcome in several studies. In the National Institutes of Health (NIH) trials comparing prednisone, azathioprine and cyclophosphamide, doubling of serum creatinine was associated with the development of renal insufficiency.[24,25] Moreover, in the Euro-Lupus Nephritis Trial a decrease of an initially elevated serum creatinine and/or decrease in proteinuria to <1 g/24 hours at six months were powerful predictors for improved long-term renal outcome.[26] A recent trial conducted by the Collaborative Study Group demonstrated that even patients with a partial response (a ≤25% increase in baseline creatinine and ≥50% reduction in baseline proteinuria to ≤1.5 g/24 hours [but >0.33 g/24 hours] within five years of entering the study) had a significantly better renal survival than patients who did not retain a response, but not as good as in patients with complete response (serum creatinine of ≤1.4 mg/dl [98 mmol/l] and proteinuria ≤0.33 g/24 hours within five years of entering the study).[27] Moreover, the choice of time-point used to address response differs in clinical studies. In the above-mentioned study, the time for attaining a complete response was significantly longer than that required to attain a partial response (median: 10.5 *vs* 5.8 months). These results are consistent with the results of other reports.[28,29] On the basis of these observations, it is comprehensible that studies with only six months of follow-up report a relatively low percentage of complete response rates.

Based on the available literature, the Dutch Working Party assigned the following definitions of response as a guide to the success of therapy (Level C):

A *complete response* includes no disease activity, i.e. proteinuria <0.5 g/24 hours, and/or a serum creatinine within 125% of the baseline value at 6 to 12 months after the start of induction therapy.

A *partial response* is defined as an improvement not sufficient for the definition of a complete response, i.e. a reduction of proteinuria of >50% (and at least <3 g/24 hours), and a serum creatinine within 125% of the baseline value at six to 12 months after the start of the induction therapy.

A *failure* of the initial induction therapy has been defined as a doubling of serum creatinine compared with the baseline value at three months after the start of induction therapy.

A *flare* is an increase in disease activity that requires intensification of the therapy and is defined as an increase of ≥25% in the lowest serum creatinine level measured during the period of induction therapy and/or the development of either a nephrotic syndrome (proteinuria >3.5 g/24 hours and serum albumin <30 g/l), while the lowest protein excretion so far has been ≤2.0 g/24 hours repeatedly, or proteinuria >1.5 g/24 hours in a previous non-proteinuric patient.

Refractory LN includes persistent or worsening renal disease activity as manifested by progressive deterioration of renal function and/or proteinuria despite optimal immunosuppressive therapy and supportive treatment, and involving at least one of the following conditions: I) failure of the initial induction treatment at three months, for which a switch to another induction therapy regime has already been carried out; II) intolerance for cyclophosphamide and mycophenolate mofetil (MMF); III) exceeding a cumulative dose of 15 gram of cyclophosphamide, IV) a second relapse within two years after start of the initial induction therapy, and V) a relative contraindication for high-dose oral or intravenous (iv) prednisone, such as avascular osteonecrosis, previous psychosis on corticosteroids, osteoporosis and/or severe obesity (BMI ≥35 kg/m^2).

TREATMENT OF LN

Induction treatment

Cyclophosphamide-containing regiments have long been considered the gold standard in inducing renal remission and preventing renal flare in patients with proliferative LN.[25,30,31] However, treatment-related toxicity raised a number of concerns.[32,33] Furthermore, while cyclophosphamide induces renal remission in a significant proportion of patients with proliferative LN, the rate of relapse is considerable.[34] In order to reduce the toxicity but not the efficacy, alternative treatment regimens have been evaluated in recent years.

In the Euro-Lupus Nephritis Trial, 90 (mainly Caucasian) patients were randomised to high-dose iv cyclophosphamide (500-750 mg/m^2 six pulses monthly, followed by two pulses tri-monthly) or low-dose iv cyclophosphamide (500 mg fixed dose, six pulses every two weeks) in combination with methylprednisolone (three days, 750 mg) followed by oral prednisone (0.5 to 1.0 mg/kg).[9,35] Following the cyclophosphamide pulses, oral azathioprine (2 mg/kg) was introduced in both treatment arms. After ten years of follow-up, no significant differences were found between the low-dose and high-dose arms with regard to survival, ESRD or doubling of serum creatinine. These data show that the 'Euro-Lupus regimen' achieves good clinical results in the long-term in an European (mainly Caucasian) population with moderately severe disease, and seems to be a good alternative for the high-dose NIH cyclophosphamide regimen, while a considerably lower cumulative dose of cyclophosphamide is given. However, it should be noticed that in the low-dose arm additional cyclophosphamide was necessary during follow-up, increasing the cumulative dose from 3.0 to 5.5 gram.

The first Dutch Lupus Nephritis Study was initiated to analyse the effect of induction therapy with either pulse iv cyclophosphamide or azathioprine combined with methylprednisolone in patients with proliferative LN.[36] In this study, cyclophosphamide was superior to azathioprine in terms of preventing renal relapse and progression of chronic lesions in repeat biopsies at 24 months. The long-term follow-up data of this study confirmed the superiority of cyclophosphamide in the prevention of renal relapses, but sustained doubling of serum creatinine, ESRD, mortality, and renal function did not differ between the two treatment groups after a median follow-up of 9.6 years.[37] These results indicate that azathioprine can not be considered to be the standard induction therapy in patients with proliferative LN and should be reserved for those patients with a strong wish to conceive and with a high risk of premature ovarian failure, who are willing to accept the higher risk of exacerbations.

The benefits of MMF for LN were first reported in uncontrolled studies of patients refractory to cyclophosphamide.[38,39] Subsequently, relatively small randomised controlled trials have been performed.[40-43] The Ginzler study, a non-inferiority RCT, demonstrated that MMF (initial dose 1 g/day, increased to 3 g/day) was significantly better in inducing complete remission (CR) at 24 weeks than the NIH-cyclophosphamide regimen (CR 22.5% *vs* 5.8% respectively).[44] In this study, 56% of the patients were Black.

In view of the small size of the MMF trials, several meta-analyses of RCTs comparing induction therapy with MMF or cyclophosphamide have been performed. The results of these analyses show that MMF appears to be superior to cyclophosphamide in terms of both response and safety (*table 2*).[45-49] However, the results of these meta-analyses should be interpreted with caution, because of the inclusion of relatively small trials, the heterogeneity for race/ethnicity, class of LN, definitions of clinical response, duration of follow-up, and MMF and cyclophosphamide dosing regimens.

Recently, the results of the Aspreva Lupus Management Study (ALMS) were reported.[50] In this superiority RCT, 370 patients with either class III, IV or V LN were randomised

Table 2. *Induction treatment: mycophenolate mofetil versus cyclophosphamide (RR or relative benefit; 95% CI)*

	Mak et al.*	Naveneethan et al.*	Walsh et al.*	Zhu et al.*	Kamanamool et al.**
PR	-	1.07 (0.72-1.60)	-	1.06 (0.71-1.59)	-
CR	-	1.36 (0.82-2.24)	-	1.81 (0.70-4.68)	1.60 (0.87-2.93)
PR/CR	1.05 (0.95-1.17)	1.15 (0.86-1.54)	-	1.20 (0.85-1.69)	1.20 (0.97-1.48)
Treatment failure	-	-	0.70 (0.54-0.90)#	-	-
ESRD	0.45 (0.18-1.12)	0.66 (0.25-1.70)	-	0.58 (0.20-1.65)	-
Death	0.71 (0.37-1.35)	0.35 (0.14-0.86)#	-	0.46 (0.17-1.30)	-
ESRD/ Death	-	-	0.44 (0.23-0.87)#	-	-
Relapse	-	-	-	-	-

***RR <1 in favour of mycophenolate mofetil; **RR >1 in favour of mycophenolate mofetil; #p<0.05 in favour of mycophenolate mofetil; RR=relative risk; CI=confidence interval; PR=partial remission; CR=complete remission; ESRD=end-stage renal disease.**

to MMF (target 3 g/day) or iv cyclophosphamide (target 0.5 to 1.0 g/m^2, six pulses monthly). Although most patients in both treatment groups experienced clinical improvement, MMF was not superior in inducing complete response at 24 weeks (MMF 56.2% and cyclophosphamide 53.0%). In addition, significant differences were not observed with regard to the rates of serious adverse events (MMF 28.0% and cyclophosphamide 23.0%) or infections (MMF 69.0% and cyclophosphamide 62.0%).

In this study, a heterogeneous population in terms of race and ethnicity was included. A subgroup analysis suggested a significantly worse response for cyclophosphamide in non-Asian, non-Caucasian mainly Black patients (MMF 60.4% *vs* cyclophosphamide 38.5%).[51] These findings seem consistent with the results of the Ginzler study where a greater proportion of Black patients were included than in the ALMS study (61.0% *vs* 25.9%).[44] So far, although MMF seems to be superior to cyclophosphamide in the high-risk Black patients, the efficacy of MMF in patients with other ethnicities seems to be comparable with cyclophosphamide.

Taking these studies together, although long-term data are not available, MMF seems to be a reasonable treatment alternative to high-dose iv cyclophosphamide in LN.

As only 60% of the patients with proliferative LN obtain a partial or complete response at 6 to 12 months in the studies discussed so far, new immunosuppressive therapies have been instituted. Given the substantial evidence for the role of B cells in the pathogenesis of SLE and the recent development of monoclonal antibodies to B-lymphocyte-specific targets, B-cell depletion seems to be an attractive approach in LN treatment. Several small, open-label uncontrolled studies suggested that rituximab may be effective in proliferative LN as initial induction therapy.[52-54] However, in contrast to these studies, two randomised, controlled trials did not show any additional significant effect of anti-CD20 as add-on therapy in patients with LN treated with MMF and corticosteroids.[55,56] Therefore, the use of rituximab as a first-line adjunctive agent in induction therapy is not justified (Level A).

Based on the results of the available literature, the Dutch Working Party proposes induction treatment in patients with proliferative LN with either the low-dose cyclophosphamide Euro-lupus regimen or MMF together with (methyl)prednisolone (Level A), as outlined in these protocols (*tables 3 and 4*).

In patients who do not meet the response criteria for partial/complete remission after 12 months of induction treatment or if induction treatment fails at three months, switch of the immunosuppressive agent from either cyclophosphamide to MMF, or from MMF to cyclophosphamide, accompanied by iv methylprednisolone (750 mg) for three days is recommended (Level C).

Table 3. *Induction treatment: mycophenolate mofetil*[50]

Mycophenolate mofetil
Week 1: 1000 mg/day
Week 2: 2000 mg/day
Week 3: 3000 mg/day
Corticosteroids
Prednisone 1 mg/kg/day, maximum 60 mg/day
After 4 weeks prednisone tapered every 4 weeks by 10 mg to 20 mg, followed by prednisone tapered every 4 weeks with 5 mg to 10 mg

Table 4. *Induction treatment: cyclophosphamide*[35]

Cyclophosphamide
A fixed dose of 500 mg iv, 6 times every two weeks
Corticosteroids
Methylprednisone pulse 750 mg iv at day 0, 1 and 2, followed by prednisone 0.5-1.0 mg/kg/day
After 4 weeks prednisone tapered every 2 weeks with 2.5 mg to 5-7.5 mg at 30 months

MAINTENANCE TREATMENT

Immunosuppressive treatment

MMF has been compared with azathioprine or tri-monthly iv cyclophosphamide as maintenance therapy in a small randomised controlled trial in non-Caucasian patients, following induction therapy with cyclophosphamide and corticosteroids. This trial showed that both MMF and azathioprine were significantly better in terms of patient survival, incidence of clinical events (death or chronic kidney failure) and prevention of relapses, if compared with cyclophosphamide.[57] However, differences between MMF and azathioprine could not be assessed due to the small number of patients included in these arms. Furthermore, it should be noted that the death rate in the cyclophosphamide arm was higher than that observed in other (NIH) studies.

Recently, two randomised, controlled trials with different study designs have been conducted to assess the optimal maintenance treatment in proliferative LN. In the MAINTAIN Nephritis Trial, MMF (2 g/day) was compared with azathioprine (2 mg/kg/day) as maintenance treatment after induction treatment with low-dose iv cyclophosphamide (Euro-Lupus regimen).[58] MMF and azathioprine were equally effective in preventing renal flares. In this study, patients were randomised at the start of the induction treatment.

Recently, data from the ALMS Maintenance Trial were published.[59] In contrast to the MAINTAIN Nephritis Trial, only patients achieving partial or complete remission during a six-month induction phase were re-randomised to corticosteroids plus MMF (2 g/day) or azathioprine (2 mg/kg/day) for up to 36 months. In this study, MMF was

superior to azathioprine in delaying the time to treatment failure, which was defined as either renal flare, necessity of rescue therapy, doubling of serum creatinine, ESRD or death (16.4% *vs* 32.4%). The completion rate at 36 months was higher in the MMF group compared with the azathioprine group (62.9% *vs* 48.6%). Superiority of MMF was consistent regardless of type of induction treatment, race or region. The discrepancy in the results between the MAINTAIN and the maintenance phase of the ALMS trial can have several explanations, such as the number of and the difference in ethnicity of the patients included in both studies, a different trial design and differences in study endpoints. Moreover, the randomisation procedure in the ALMS Maintenance Trial selected those patients with a good clinical response. As indicated before, a considerable proportion of patients do not show such a favourable response at six months.

Based on the above-mentioned studies, MMF is superior to azathioprine in maintaining a renal response and in preventing a renal flare in patients who had a response to induction therapy (Level A).

Duration of therapy

It is difficult to precisely define the criteria that allow the identification of patients in whom the dose of immunosuppression can be reduced safely. If the disease is clinically and serologically quiescent the immunosuppression could be tapered slowly. Based on the study by Grootscholten *et al*. duration of therapy of at least five years seems warranted.[60] In this context, the ten-year follow-up data of the Euro-Lupus Nephritis Trial showed that 53% of the patients were still on maintenance immunosuppressive therapy.[9] The Dutch Working Party proposes the following reduction schedule as a guidance in clinical practice (Level C): taper the dose of prednisone to 10 mg every other day at four years after the start of the induction therapy, followed by a 50% dose reduction of azathioprine/MMF six months later and continue this treatment regimen for at least two more years.[37] After this period (6.5 years), the decision to stop immunosuppressive treatment will be left to the discretion of the treating physician and the patient. This advice differs from the tapering schedule as proposed in the ALMS and MAINTAIN trial. In the ALMS trial the dose of corticosteroids was maximally 10 mg until 36 months with no data after 36 months. In the MAINTAIN trial prednisone was dosed at 7.5 mg at six months, 5 mg at 12 months, with further tapering after 24 months.[58,59] There are no data available from controlled studies allowing clearer advice.

Supportive treatment

The importance of concomitant immune modulation with hydroxychloroquine has been highlighted by several recently published studies demonstrating lower rates of renal flare, ESRD and mortality in those patients taking hydroxychloroquine.[61-64] Therefore, unless there are contraindications, the consensus opinion is that all patients should receive hydroxychloroquine (200 to 400 mg) from the start of the induction therapy onwards (Level B). To detect retinal toxicity a baseline examination within the first year of use and an annual screening after five years of use should be performed by an ophthalmologist. For patients with maculopathy or additional risk factors for retinal toxicity (cumulative dose of hydroxychloroquine >1000 g, elderly, kidney and/or liver dysfunction) annual screening should be performed from the initiation of the therapy.[65]

In patients with LN, the indication for supportive treatment depends on the stage of chronic kidney disease and the presence of proteinuria. In general, the strategy aims at reduction of cardiovascular risk factors and should comprise lifestyle modifications (smoking cessation, weight reduction if BMI >25 kg/m^2, increased physical activity and dietary changes, especially salt restriction) together with adequate control of blood pressure (target of <130/80 mmHg, Level A for proteinuria >1 g/24 hours) with angiotensin inhibitors (ACEi) or angiotensin receptor blockers (ARBs) (Level A for proteinuria >1 g/24 hours), and treatment of hyperlipidaemia (Level C). As for stage 3 to 5 chronic kidney disease (creatinine clearance <60 ml/min), treatment options are summarised in *table* 5.[66]

To reduce the risk of corticosteroid-induced osteoporosis each patient should receive calcium and vitamin D supplementation. In addition, a bisphosphonate should be started in each patient receiving >15 mg/day prednisone, or in postmenopausal women and males >70 years of age using prednisone in a dosage of 7.5 to 15 mg/day (see CBO Consensus Osteoporosis 2011).[67] However, in patients with renal failure (creatinine clearance <60 ml/min) and in patients with a pregnancy wish, bisphosphonates should not be given.[67] In addition to the supportive treatment options mentioned above,

Table 5. *Supportive treatment in chronic kidney disease stage 3-5*[66]

Blood pressure
Dietary sodium reduction (5.0 g sodium chloride)
Achieve blood pressure <130/80 mmHg, using an ACEi or ARB as first-line treatment in the presence of >1 g/day of proteinuria
Proteinuria
Achieve proteinuria <1 g/day, using an ACEi or ARB as first-line treatment
Low protein diet (0.8 g/kg body weight per day)
Lipids
Achieve LDL cholesterol <2.6 mmol/l, using statins as first-line treatment

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LDL = low-density lipoprotein.

low-dose acetylsalicylic acid seems warranted in patients with positive anti-phospholipid antibodies for primary prevention of thrombosis and pregnancy loss (Level C).[12] Moreover, coumarines should be considered in patients with a nephrotic syndrome and a serum albumin <20 g/l (Level C).[68]

Treatment of refractory LN

The evidence for any kind of immunosuppressive therapy in refractory LN is weak. Small observational studies provided evidence that rituximab seems to be an effective treatment for patients with active LN that is refractory to standard immunosuppressive therapy.[52,53,69-73] However, the use of the different dosing schedules in these observational studies make an interpretation difficult.[54] Adjunctive treatment with tacrolimus resulted in a significant clinical response in patients resistant to MMF.[74-76] However, although these newly introduced immunosuppressive regimens have proven their efficacy in some cases of refractory LN, the application of high-dose cyclophosphamide (NIH regimen) could still be a possibility. These (adjunctive) regimens are described in *table 6 (*Level C).

INDICATIONS FOR REPEAT BIOPSY IN PATIENTS TREATED FOR CLASS III/IV LN

The benefit of a repeat biopsy during the disease course of proliferative LN is questionable since there is no consensus in the literature. A recent retrospective study showed that in the presence of proliferative lesions in the original biopsy, a repeat biopsy during a clinical flare is not necessary as these patients rarely switch to a pure non-proliferative LN.[77] Moreover, histopathological variables in a protocolised biopsy at two years after induction therapy did not predict renal outcome at 77 months or at 115 months in patients with proliferative LN randomised to iv cyclophosphamide or azathioprine/methylprednisolone.[37,78] In contrast to these findings, Hill *et al*. reported that certain histological findings in repeat biopsies at six months had a better predictive power for subsequent doubling of serum creatinine than the same markers in the initial biopsy.[79]

Given the conflicting results from the literature, the opinion of the Dutch Working Party is that a repeat biopsy is only justified in those patients where it is anticipated that the findings have therapeutic consequences (Level C). First, the persistence of proteinuria after reaching a partial response, despite optimal supportive treatment including salt restriction and treatment with ACEi or ARBs to differentiate between active disease, chronic lesions or transition to focal segmental glomerulosclerosis. Second, failure to respond (either complete or partial response) at 12 months after the start of the initial induction treatment to differentiate between active and chronic lesions.

Table 6. *Treatment of refractory lupus nephritis*

Rituximab*
1000 mg intravenous at day 1 and 15 as add-on therapy
Tacrolimus*[75]
0.1 mg/kg/day, through level 4-10 µg/l as add-on therapy
Cyclophosphamide*[25]
750 mg/m^2 intravenous, increased with 250 mg per dose to a maximum of 1500 mg 6 times monthly, then every 3 months for an additional 2 years
***Prednisone 1 mg/kg/day, maximum 60 mg/day.**

CONCLUSION

In this report guidelines are proposed for the management of proliferative LN, with regard to the following topics: indications for a first renal biopsy, definitions of treatment response, selection of treatment options, and indications for repeat biopsy. This consensus approach provides agreed expert opinion for clinicians and will hopefully support the optimisation of treatment in patients with proliferative LN. Moreover, following this guideline throughout the Netherlands could be a basis for future central registration and follow-up on a national level.

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REFERENCES

1. Berden JHM, Licht R, Bruggen MCJ, et al. Role of nucleosomes for induction of glomerular binding of auto-antibodies in lupus nephritis. Opin Nephrol Hypertens. 1999;8:299-306.
2. Berden JH. Lupus Nephritis. Kidney Int. 1997;52:538-58.
3. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus. 2006;15:308-18.
4. Austin HA. Clinical evaluation and monitoring of lupus kidney disease. Lupus. 1998;7:618-21.
5. Cameron JS. Lupus nephritis. J Am Soc Nephrol. 1999;10:413-24.
6. Bastian HM, Roseman JM, McGwin G Jr. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. Lupus. 2002;11:152-60.
7. Derksen RHWM, Hené RJ, Kater L. The long-term clinical outcome of 56 patients with biopsy-proven lupus nephritis followed at a single centre. Lupus. 1992;1:97-103.
8. Donadio JV, Hart GM, Bergstrath EJ, Holley KE. Prognostic determinants in lupus nephritis: a long-term clinic-pathologic study. Lupus. 1995;4:109-15.

9. Houssiau FA, Vasconcelos C, D'Cruz D. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis. 2010;69:61-4.

10. Appel GB, Cohen DJ, Pirani CL, Meltzer JI, Estes D. Long-term follow-up of patients with lupus nephritis. A study based on the classification of the World Health Organization. Am J Med. 1987;83:877-85.

11. Austin HA III, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcome in severe lupus nephritis: contributions of clinical and histological data. Kidney Int. 1994;45:544-50.

12. Bertsias G, Ioannidis JPA, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics. Ann Rheum Dis. 2008;67:195-205.

13. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004;65:521-30.

14. Mahajan SK, Ordonez NG, Feitelson PJ, Lim VS, Spargo BH, Katz AI. Lupus nephropathy without clinical renal involvement. Medicine. 1977;56:493-500.

15. Faurschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. J Rheum. 2006;33:1563-9.

16. Contreras G, Pardo V, Cely C, et al. Factors associated with poor outcomes in patients with lupus nephritis. Lupus. 2005;14:890-5.

17. Gladman DD, Urowitz MB, Cole E, Ritchie S, Chang CH, Churg J. Kidney biopsy in SLE. I. A clinical-morphologic evaluation. Q J Med. 1989;73:1125-33.

18. Nossent JC, Henzen-Logmans SC, Vroom TM, Huysen V, Berden JH, Swaak AJ. Relation between serological data at the time of the biopsy and renal histology in lupus nephritis. Rheum Int. 1991;11:77-82.

19. Berden JHM, Assman KJM. Renal involvement in collagen vascular diseases and dysproteinemias. Atlas of Diseases of the kidney. Vol IV.1999.Blackwell Science. Editor S. Klahr.

20. Tektonidou MG, Sotsiou F, Nakopoulou L, Vlachoyiannopoulos PG, Moutsopoulos HM. Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: prevalence, clinical associations, and long-term outcome. Arthritis Rheum. 2004;50:2569-79.

21. Singh JA, Solomon DH, Dougados M, et al. Development of classification and response criteria for rheumatic diseases. Arthritis Rheum. 2006;55:348-52.

22. Bertsias G, Gordon C, Boumpas DT. Clinical trial in systemic lupus erythematosus (SLE): lessons from the past as we proceed to the future — the EULAR recommendations for the management of SLE and the use of end-points in clinical trials. Lupus. 2008;17:437-42.

23. Gordon C, Bertsias G, Ioannidis JPA, et al. EULAR points to consider for conducting clinical trials in systemic lupus erythematosus. Ann Rheum Dis. 2009;68:470-6.

24. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum. 1991;605-7.

25. Gourley MF, Austin III HA, Scott D, et al. Methylprednsiolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. Ann Int Med. 1996;125:549-57.

26. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: Arthritis Rheum. 2004;50:3934-40.

27. Chen YE, Korbet SM, Katz RS, et al. Value of complete or partial remission in severe lupus nephritis. Clin J Am Soc Nephrol. 2008;3:46-53.

28. Chan TM, Tse KC, Tang CS, Lai KN, Li FK. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone. Lupus. 2005;14:265-72.

29. Ioannidis JP, Boki KA, Katsorida ME, et al. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophophamide. Kidney Int. 2000;57:258-64.

30. Austin HA III, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Eng J Med. 1986;314:614-9.

31. Boumpas DT, Astin III AH, Vaughan EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophophamide in severe lupus nephritis. Lancet. 1992;340:741-5

32. Boumpas DT, Austin HA III, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk for sustained amenorrhea with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Int Med. 1993;119:366-9.

33. Petri M. Prospective study of systemic lupus erythematosus pregnancies. Lupus. 2004;13:688-9.

34. Bansal VK, Beto JA. Treatmnet of lupus nephritis: a meta-analysis of clinical trials. Am J Kidney Dis. 1997;29:193-9.

35. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis. The Euro-Lupus Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002;46:2121-31.

36. Grootscholten C, Ligtenberg G, Hagen EC, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int. 2006;70:732-42.

37. Arends S, Grootscholten C, Derksen RHWM, et al. Long-term follow-up of a randomized controlled trial of azathioprine/methylprednisolone versus cyclophophamide in patients with proliferative lupus nephritis. Ann Rheum Dis. 2011, nov 29 (Epub ahead of print).

38. Gaubitz M, Schorat A, Schotte A, Kern P, Domschke W. Mycophenolate mofetil for the treatment of systemic lupus erythematosus: an open pilot trial. Lupus. 1999;8:731-6.

39. Dooley MA, Cosio FG, Nachman PH, et al. Mycophenolate mofetil therapy in lupus nephritis: clinical observations. J Am Soc Nephrol. 1999;10:833-9.

40. Chan TM, Li FK, Tang CSO, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. N Engl J Med. 2000;343:1156-62.

41. Chan TM, Tse K-C, Tang CS-O, et al. Long-term study of mycophenolate mofetil versus continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol. 2005;16:1076-84.

42. On LM, Hooi LS, Lim TO, et al. andomized controlles trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrol. 2005;10:504-10.

43. Hu W, Liu Z, Chen H, et al. Mycophenolate mofetil versus cyclophosphamide therapy for patients with proliferative lupus nephritis. Chin Med J. 2002;115:705-9.

44. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Eng J Med. 2005;353:2219-28.

45. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR. Mycophenolate mofetil for induction therapy of lupus nephritis: a systemic review and meta-analysis. Clin J Am Soc Nephrol. 2007;2:968-75.

46. Zhu B, Chen N, Lin Y, et al. Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2007;22:1933-42.

47. Naveneethan SD, Viswanathan G, Strippoli GF. Treatment options for proliferative lupus nephritis: an update of clinical trial evidence. Drugs. 2008;68:2095-2104.

48. Mak A, Cheak AAC, Tan JYS, Su HC, Ho RCM, Sing Lau C. Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression. Rheumatology. 2009;48:944-52.

49. Kamanamool N, McEvoy M, Attia J, Ingsathit A, Ngamjanyaporn P, Thakkinstian A. Efficacy and adverse events of mycophenolate mofetil versus cuclophosphamide for induction therapy of lupus nephritis. Systemic review and meta-analysis. Medicine. 2010;89:227-35.

50. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophophamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009;20:1103-12.