Current Rheumatology Reports (2020) 22: 30
https://doi.org/10.1007/s11926-020-00906-7

SYSTEMIC LUPUS ERYTHEMATOSUS (G TSOKOS, SECTION EDITOR)

An Update on the Diagnosis and Management of Lupus Nephritis

Myrto Kostopoulou[1] · Christina Adamichou[2,3] · George Bertsias[3,4]

Published online: 4 June 2020

Abstract

Purpose of Review Update on the diagnosis, treatment, and monitoring of lupus nephritis.

Recent Findings The recent criteria enable the earlier classification of lupus nephritis based on kidney biopsy and compatible serology. Treatment of active nephritis includes low-dose intravenous cyclophosphamide or mycophenolate, followed by maintenance immunosuppression. Recent trials have suggested superiority of regimens combining mycophenolate with either calcineurin inhibitor or belimumab, although their long-term benefit/risk ratio has not been determined. Encouraging results with novel anti-CD20 antibodies confirm the effectiveness of B cell depletion. Achievement of low-grade proteinuria (< 700–800 mg/24 h) at 12-month post-induction is linked to favorable long-term outcomes and could be considered in a treat-to-target strategy. Also, repeat kidney biopsy can guide the duration of maintenance immunosuppression. Lupus nephritis has increased cardiovascular disease burden necessitating risk-reduction strategies.

Summary An expanding spectrum of therapies coupled with ongoing basic/translational research can lead to individualized medical care and improved outcomes in lupus nephritis.

Keywords Systemic lupus erythematosus · Risk stratification · Therapeutic target · Flares · Biologic agents · Comorbidities

Introduction

Renal involvement represents a severe complication of Systemic Lupus Erythematosus (SLE) and biopsy-proven lupus nephritis (LN) occurs in 20–40% of patients [1–3]. The management of LN has witnessed advances over the past decades thus resulting in improved outcomes [4, 5]. Still, a considerable proportion (10–30%) of patients will develop chronic renal insufficiency and/or end-stage renal disease (ESRD) [3, 6–9]. In addition, LN and ESRD are associated with reduced health-related quality of life [3, 10], increased healthcare utilization and medical costs [11], comorbidities [12, 13], and most importantly, 6- to 26-fold increased mortality compared with the general population [8, 14].

In agreement with earlier studies, recent data have highlighted a number of factors that are associated with worse prognosis in LN, such as male gender, non-white race, class IV (with or without concomitant class V) disease (especially IV-global subtype [15]), arterial hypertension, low glomerular filtration rate (GFR), increased histological activity, and chronicity lesions (Table 1) [4, 16, 17]. Notably, tubulointerstitial lesions such as tubulitis, interstitial fibrosis, and tubular atrophy [17–19], as well as thrombotic microangiopathy [20], are increasingly recognized as risk factors for progression into ESRD, whereas the significance of serology is less clear [21]. Although appreciation of the prognostic impact of the aforementioned factors offers the possibility for patient-tailored medical care, still, the management of LN is rather generic. In this review, we summarize recent evidence pertaining to the diagnosis, therapy, and monitoring of LN, including special issues such as the treatment of pediatric LN,

This article is part of the Topical Collection on *Systemic Lupus Erythematosus*

✉ George Bertsias
gbertsias@uoc.gr

1 4th Department of Internal Medicine, Attikon University Hospital, Joint Rheumatology Program, National and Kapodistrian University of Athens Medical School, Athens, Greece

2 4th Department of Internal Medicine, Hippokration University Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

3 Department of Rheumatology, Clinical Rheumatology and Allergy, University of Crete Medical School, 71008 Voutes-Stavrakia, Heraklion, Greece

4 Laboratory of Rheumatology, Autoimmunity and Inflammation, Institute of Molecular Biology and Biotechnology-FORTH, Heraklion, Greece

Table 1 Major risk factors associated with adverse renal outcomes in patients with lupus nephritis

Adverse renal outcome			
Risk factors	Lower rates of complete response	Renal flares	Progression to chronic kidney disease/end-stage renal disease
Demographic			• Non-white race • Older age
Kidney biopsy	• Class IV nephritis • High activity index; ≥ 50% crescents • High chronicity index; glomerular sclerosis	• Class IV nephritis • High activity index; endocapillary proliferation	• Class IV nephritis • High activity index; crescents; fibrinoid necrosis • High chronicity index; glomerular sclerosis; interstitial fibrosis; tubular atrophy • Thrombotic microangiopathy
Serology	• High anti-dsDNA titres post-induction • High anti-C1q titres		• Positive anti-neutrophil cytoplasmic antibodies (ANCA)
Clinical			• Hypertension • Higher serum creatinine • Failure to achieve complete renal response

during pregnancy, and ESRD. Notwithstanding the lack of comparative data, we provide some guidance with regard to appropriate treatment regimen based on the clinical scenario. (Table 2)

Early Diagnosis of Lupus Nephritis

Delay in diagnosis of LN and initiation of immunosuppressive treatment have been linked to lower renal response and increased ESRD rates [16, 22, 23]. Accordingly, vigilance is required for the prompt identification of signs and symptoms suggestive of kidney disease. To facilitate early classification/diagnosis, the 2012 Systemic Lupus Collaborating Clinics (SLICC) [24, 25] and the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) [26•] classification criteria enable the classification of SLE based merely on histological evidence of LN coupled with positive ANA or lupus autoantibodies. Notably, a study evaluating cases diagnosed with LN from 1970 to 2016 found decreasing trends of renal insufficiency and histological chronicity, and increasing rates of isolated urinary abnormalities at the time of LN presentation [4], all suggestive of tendency for early than delayed diagnosis. In the same study, an increase in patient age and longer time elapsing between SLE onset and LN occurrence was observed towards more recent times, which might be due to improved disease management [27].

To this end, risk factors for incident LN include younger age, male gender, non-white race, high anti-dsDNA titer, and presence of anti-Sm antibody [28]. Anti-C1q antibodies have also been shown to predict active proliferative LN with high specificity; however, they lack standardization and are not universally assayed [29, 30]. Importantly, patients with LN are characterized by higher genetic burden [31, 32] and neutrophil gene signature in the peripheral blood [33, 34], which could help to define high-risk groups among SLE patients [35] and possibly implement preventative strategies.

Treatment of Proliferative Lupus Nephritis: an Expanding Range of Therapeutic Regimens

New Data on the Efficacy and Safety of Conventional Immunosuppressive Regimens

At present, first-line treatment of active proliferative (class III or IV, with or without concomitant class V) nephritis includes the combination of high-dose glucocorticoids (typically, pulses of intravenous methylprednisolone followed by 0.5 mg/kg/day oral prednisone) with either low-dose cyclophosphamide (500 mg intravenous bolus administered bi-weekly for 3 months) or oral mycophenolate (2 to 3 g/day, for 6 months) [36–38]. Following this initial period ("induction phase"), less intensive therapy with gradually tapered dose of glucocorticoids and either mycophenolate (1 to 2 g/day) or azathioprine (2 mg/kg/day) is administered for several years to consolidate and maintain the response ("maintenance phase"). The aforementioned recommendation is supported by randomized controlled trials (RCTs) demonstrating comparable efficacy and more favorable toxicity profile of low-dose cyclophosphamide and mycophenolate compared with the high-dose cyclophosphamide regimen [39, 40].

According to a recent Cochrane Collaboration Group systematic review and meta-analysis of RCTs, mycophenolate is as effective as intravenous cyclophosphamide in inducing remission in LN (8 studies, 828 participants; relative risk [RR] 1.17, 95% confidence interval [CI] 0.97 to 1.42) [41•]. Additional observational studies have suggested efficacy of mycophenolate across different ethnic groups [42, 43], and in terms of certain long-term outcomes such as chronic kidney disease and renal flares [44, 45]. Notwithstanding, a post hoc analysis of a controlled trial showed that induction with intravenous cyclophosphamide versus mycophenolate was associated with a lower

Table 2 Therapeutic regimens in lupus nephritis

Low-dose intravenous cyclophosphamide	• Most extensively studied in white patients and in proliferative lupus nephritis • Very low risk for gonadal toxicity • Long-term efficacy data are available • Maintenance with either mycophenolate or azathioprine
Mycophenolate	• Efficacy confirmed across diverse ethnic backgrounds • Long-term efficacy data are still limited • Used both as induction and maintenance treatment • Switch to azathioprine is associated with increased risk for flares
High-dose intravenous cyclophosphamide	• Reserved for very high-risk patients • Age- and dose-dependent risk for gonadal toxicity • Long-term efficacy data are available • Maintenance with either mycophenolate (lowest incidence of flares) or azathioprine
Mycophenolate combined with calcineurin inhibitors	• Faster reduction of proteinuria; increased rates of renal response • Most extensively studied in Asian patients • Long-term safety remains to be determined • Mycophenolate should be used at lower dose to reduce risk for infections • Possible indications: severe nephrotic syndrome at baseline; extensive podocytopathy at kidney biopsy; inadequate or slow reduction of proteinuria while on treatment with mycophenolate
Mycophenolate combined with belimumab	• Published data not yet available • Possible indications: inadequate or slow reduction of proteinuria while on treatment with mycophenolate; relapsing disease; inability to taper off glucocorticoids; extra-renal lupus activity
Rituximab/B cell depleting agents	• Randomized evidence is not available (rituximab) or is pending (novel anti-CD20 monoclonal antibodies) • Monotherapy or in combination with other immunosuppressant • Used both as induction and maintenance treatment • Possible indications: refractory or relapsing disease

likelihood of treatment failure after 3 years (odds ratio 0.50; 95% CI 0.2 to 1.0) [21]. To this end, more evidence is still needed with regard to the long-term efficacy of mycophenolate especially against "hard" renal outcomes.

Low-dose intravenous cyclophosphamide, followed by maintenance with azathioprine or mycophenolate, has yielded long-term (10 years) effectiveness against ESRD, yet the majority of patients will require chronic treatment with immunosuppressive agents and low-dose glucocorticoids [46, 47]. More recently, the regimen has been successfully used in non-Caucasians including Asians [42], Africans [48], and African-Americans [49], although this has not always been confirmed [50–52]. According to the present treatment paradigm, high-dose cyclophosphamide should be reserved for selected severe cases such as with nephritic urine sediment and impaired renal function, or histological crescents or necrosis affecting > 25% of glomeruli [36].

Calcineurin Inhibitors: Comeback in Lupus Nephritis

Several studies have recently explored the efficacy of calcineurin inhibitors (CNI), namely tacrolimus, cyclosporin, and voclosporin, either as monotherapy or in combination with mycophenolate. A meta-analysis of five RCTs showed that tacrolimus was more effective than intravenous cyclophosphamide at inducing complete renal remission (RR 1.59; 95% CI 1.16 to 2.19), although the difference was non-significant when mycophenolate was used as comparator (RR 0.97; 95% CI 0.64 to 1.46) [53]. Similarly, tacrolimus was non-inferior to mycophenolate in a trial involving 150 Asian patients with extended follow up. At 5 years, the cumulative incidence of a composite outcome (decline of creatinine clearance by at least 30%, development of chronic kidney disease or death) was comparable between the two groups [54•].

The combination of mycophenolate with CNI and glucocorticoids (multitarget regimen) has recently drawn attention in LN. Notably, a large RCT comparing mycophenolate (1 g/day) plus tacrolimus (4 mg/day) against intravenous cyclophosphamide (0.75 mg/m^2, 6 monthly boluses)—both given on a background of glucocorticoids—in 368 Chinese patients with LN reported nearly 2-fold higher remission rates with the former regimen at 24 weeks [55]. Notwithstanding the aforementioned data are limited by the inclusion of almost exclusively Asian patients, results from the multi-ethnic phase 2 [56•] and phase 3, https://ir.auriniapharma.com/press-releases/detail/164/aurinia-announces-positive-aurora-phase-3-trial-results. https://ir.auriniapharma.com/press-releases/detail/164/aurinia-announces-positive-aurora-phase-3-trial-results. controlled trials of voclosporin/mycophenolate versus mycophenolate alone have confirmed the superior efficacy (OR 2.65; 95% CI 1.64 to 4.27) with acceptable safety of the multitarget regimen, at least at the short-term. To this end, it remains unclear as to whether the multitarget regimen should be viewed as a universal first-line treatment of LN, or whether it should be considered for selected patients such as

those with severe nephrotic syndrome or podocytopathy at presentation, or with inadequate reduction in proteinuria after initial treatment with mycophenolate [38••]. Skepticism against their use pertains to the fact that CNIs may exert predominantly antiproteinuric—rather than immunomodulatory—effects, as well as their possible nephrotoxicity with long-term use [57].

Biologics in Lupus Nephritis

Despite its failed trial, B cell depletion with rituximab (anti-CD20 monoclonal antibody) has shown promising results in numerous non-randomized LN studies, especially when used as salvage therapy [50]. Renal response rates approximate 70% (40% complete, 30% partial response) and correlate positively with complete (OR 5.8) and long-lasting (> 71 days; OR 4.1) B cell depletion, and negatively with longer time to achieving depletion (OR 0.89) [58], thus suggesting that monitoring peripheral B cell counts might be a useful biomarker [59]. Blissfully, obinutuzumab, a humanized anti-CD20 monoclonal antibody, is currently evaluated in a phase 3 trial (NCT04221477) based on encouraging results when used in combination with mycophenolate, https://www.roche.com/media/releases/med-cor-2019-11-11b.htm. https://www.roche.com/media/releases/med-cor-2019-11-11b.htm. Moreover, ofatumumab, another human monoclonal antibody against CD20, has been successfully used instead of rituximab in cases of intolerance/immunogenicity to the latter [60].

Belimumab, a monoclonal antibody targeting BAFF (B cell activating factor) currently approved for the treatment of active SLE, has also yielded evidence for efficacy in renal disease [61]. Interestingly, BAFF has been implicated in LN by inducing renal tertiary lymphoid structures and regulating the position of intra-glomerular T lymphocytes [62]. Indeed, the Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis (BLISS-LN) trial was recently announced to meet its primary endpoint demonstrating increased renal response rates over 2 years in patients who received belimumab compared with placebo (both combined with standard therapy) (43% versus 32%, $p = 0.031$), https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-headline-results-in-phase-3-study-of-benlysta-in-patients-with-lupus-nephritis/. https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-headline-results-in-phase-3-study-of-benlysta-in-patients-with-lupus-nephritis/. A detailed look at the results of this trial, once published, will be needed in order to determine the position of belimumab in the therapeutic armamentarium of LN. To this end, belimumab could be considered add-on therapy to mycophenolate in cases of inadequate renal response, inability to taper off prednisone to less than 7.5 mg/day, and/or presence of extra-renal lupus activity [63]. Finally, anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1, has demonstrated efficacy in SLE [64•] and its efficacy in LN is currently being assessed (NCT02547922).

Maintenance Treatment in Lupus Nephritis: For how Long?

The two landmark RCTs of maintenance immunosuppressive treatment in proliferative LN, the MAINTAIN trial [46] and the Aspreva Lupus Management Study (ALMS) [65], despite differences in their design and the induction regimens, both provided evidence for the long-term efficacy of mycophenolate and azathioprine. Notably, in a meta-analysis of 4 RCTs including 452 LN patients, treatment with azathioprine was associated with increased risk of relapse as compared with mycophenolate (RR 1.75; 95% CI 1.20 to 2.55) although the two regimens did not differ in terms of ESRD or mortality [41•]. Based on these results, mycophenolate may be preferred over azathioprine in severe LN cases or when the former drug was also used for induction [66]. Limited data support the use of CNIs as maintenance treatment in proliferative LN [67], still they can be a useful option in cases of pregnancy or intolerance to other agents. Finally, a controlled study in Asian patients has demonstrated efficacy of a multitarget-based maintenance regimen (mycophenolate 0.5–0.75 g/day, tacrolimus 2–3 mg/day) however, in combination with unacceptably high dose of prednisone (10 mg/day) over a period of 18 months [68].

To date, there is no study designed to evaluate the feasibility of discontinuing immunosuppressive therapy in LN. In a retrospective analysis of 73 Caucasian LN patients who achieved remission, successful (i.e., free of renal relapse) withdrawal of immunosuppressives was accomplished in 71.2% of cases, particularly those with longer treatment duration (average 98.1 versus 31.0 months in cases who relapses) and longer period on remission (52.8 versus 12.0 months) [69]. Accordingly, treatment should be maintained for at least 3 to 5 years after remission has been achieved, although it may be extended in patients with adverse prognostic factors such as African ancestry, renal flares, and chronic kidney disease. Interestingly, among patients with clinically quiescent LN who underwent per-protocol repeat kidney biopsy, the risk for relapse during the ensuing 24 months was found to be independently associated with the histological activity score [70•], suggesting that kidney biopsy might be used to guide duration of maintenance treatment in LN [71].

Treatment of Membranous Lupus Nephritis

Patients with pure class V (membranous) LN and nephrotic-range proteinuria may benefit from immunosuppressive treatment such as mycophenolate or high-dose intravenous cyclophosphamide, in combination with glucocorticoids [36].

Other options have also been used albeit supported by less evidence. Specifically, low-dose cyclophosphamide was evaluated in a small RCT yielding comparable response rates with mycophenolate (71.4% versus 66.7%, respectively) [42•]. A network meta-analysis of RCTs and cohort studies has also suggested efficacy of CNIs in membranous LN [72], which however, are considered second-line agents for induction or maintenance therapy due to their safety profile and the need for prolonged administration to prevent relapses [73]. Similar to proliferative nephritis, the multitarget regimen consisting of mycophenolate, tacrolimus, and glucocorticoids demonstrated superior short-term efficacy than intravenous cyclophosphamide and glucocorticoids in a subgroup of 69 Chinese patients with class V LN (response rates 33.1% versus 7.8%, respectively) [55]. Finally, a small retrospective study reported high renal response rates (13 out of 15 patients) of rituximab used in combination with glucocorticoids [74], although this option is typically reserved for refractory/relapsing cases.

Monitoring Lupus Nephritis

Treat-to-Target

The present paradigm in the management of rheumatic diseases has introduced the concept of "treating-to-target" towards improvement of long-term disease and patient prognosis [75]. In clinical practice, assessment of the renal response to treatment can be challenging as it encompasses a variety of relevant parameters such as GFR, proteinuria, urinalysis, serological markers, blood pressure, body weight, hematocrit, and serum albumin [36]. Among these, changes in proteinuria have been identified as the best individual predictor of long-term renal outcomes [76]. Accordingly, a complete renal response is typically defined as a decrease in proteinuria to very low levels (less than 500 mg/24 h) coupled with normalization or stabilization (within 10% of normal GFR if previously abnormal) of renal function, with or without clearance of abnormal urinary sediment. This state has been consistently associated with favorable long-term renal prognosis in the context of RCTs and long-term observational studies [77–81], and therefore, is considered the ultimate therapeutic goal in LN [36, 38, 66]. Attainment of more stringent proteinuria cut-offs (< 150 mg/24 h) is associated with even lower risk of 5-year renal flare rate and development of chronic kidney disease, but it may be less frequently encountered [82].

In addition, post hoc analysis of the low-dose intravenous cyclophosphamide RCTs has indicated that proteinuria below 700–800 mg/24 h at 12 months following treatment initiation predicts favorable long-term renal outcome with sensitivity 71–81% and specificity 75–78% [76, 83]. Importantly, the prognostic value of proteinuria < 800 mg/24 h at 12 months was confirmed (sensitivity 90%, specificity 78%, negative predictive value 94%) in a long-term observational study of 94 patients with biopsy-proven LN [84]. Collectively, these data suggest that treatment in LN should aim at a proteinuria level below 700–800 mg/24 h at 12 months and below 500 mg/24 h at 24 months [38, 77, 78]. Interim goals at 3 to 6 months should include a consistent decrease in proteinuria by at least 25–50% [85]. Although normalization of anti-dsDNA soon after induction treatment has also been linked to favorable renal response [21], therapeutic adjustments based on serological markers alone are currently not recommended.

Defining Refractory and Relapsing Disease and the Role of Repeat Kidney Biopsy

Although early resolution of proteinuria is associated with excellent prognosis, data from RCTs suggest that only 25–40% of LN patients will achieve complete renal response within the first 6 months since treatment initiation [86, 87]. Indeed, it has long been appreciated that therapy-induced clearance of kidney immune deposits and inflammation is a chronic process and that heavier baseline proteinuria takes longer to resolve [88]. In accordance, the proportion of treated LN patients who meet the renal response criteria may increase over time [89]: therefore, monitoring the kinetics of proteinuria may be more appropriate indicator of the effectiveness of immunosuppressive treatment. Still, a considerable proportion (20–30%) of patients will response poorly or inadequately to first-line treatment, which is associated with increased risk for ESRD [78, 90].

Exacerbation of LN in a patient who previously responded to treatment represents yet another adverse outcome, and a contemporary observational study found that renal relapse-free survival rate was 69% and 57% at 5 and 10 years, respectively, post induction treatment [45]. Renal flares can be classified as proteinuric or nephritic (i.e., accompanied by decrease in GFR by ≥ 10% and re-activation of urine sediment) [91], the latter carrying the highest risk for progression into ESRD [92, 93]. Serologic reactivation may predate renal flares [94]; however, pre-emptive treatment is currently not recommended.

In the context of refractory or relapsing LN, (repeat) kidney biopsy may be particularly useful to evaluate the histological class, activity, and chronicity lesions, exclude other pathologies, and provide therapeutic guidance [95]. Notably, several studies have highlighted a clinical–histological discordance in patients with clinically quiescent LN [96, 97], and that persistence of histologically active disease in spite of reduced proteinuria is associated with increased likelihood for renal relapse upon treatment withdrawal [70, 98]. Together, these findings suggest the possibility of using per-protocol kidney biopsy to determine the optimal intensity and duration of maintenance immunosuppressive therapy in LN [71],

although this will require further validation in prospective studies.

Treatment of Refractory and Relapsing Lupus Nephritis

For patients with refractory LN and following assessment of medication adherence, the usual approach includes switching to another first-line treatment, for instance, from mycophenolate to cyclophosphamide (including the high-dose regimen) and vice versa, although there is limited supporting evidence [99, 100]. CNIs, particularly as part of multitarget regimens, represent another option [101, 102], especially in the absence of significant renal fibrosis. B cell depleting agents have been extensively used off-label in LN refractory to one or more conventional immunosuppressive agents. In a meta-analysis of three studies including 57 LN patients with refractory disease, treatment with rituximab induced renal response in 70% (95% CI 55% to 81%), and this was accompanied by a steroid-sparing effect (mean reduction: 12.5 mg/day; 95% CI 6.4 to 18.6) [103]. Finally, addition of belimumab to background mycophenolate could also be considered although evidence regarding the effectiveness of this combination in refectory cases is still limited [61].

The management of a LN relapse will depend on its severity (increase in proteinuria, reduction in GFR, histological findings in case of repeat biopsy) and the possible co-existence of extra-renal lupus activity. There is paucity of evidence but in general, therapeutic measures include initiation or increase in glucocorticoids (including pulses of intravenous methylprednisolone), re-induction with any of the available agents, or using the same regimens as described above for refractory LN [100, 104–106]. To this end, considering the lack of randomized evidence and head-to-head comparisons, treatment of relapsing or refractory nephritis cannot follow the "one size fits all" rule. For patients who are on mycophenolate and manifest inadequate renal response, a CNI or belimumab can be added, the latter being preferred if there is history of flares or generalized SLE activity. In the scenario of a severe relapse, induction with cyclophosphamide or rituximab may be considered.

Lupus Nephritis in Special Patient Groups

Pediatric Lupus Nephritis

Childhood-onset LN tends to have more aggressive presentation, often leading to earlier and higher damage accrual. Evidence on its management is mainly extrapolated from studies in adults. A kidney biopsy offers a definitive diagnosis and guides therapeutic decisions. Similar to adult LN, the therapeutic goal is complete or partial renal response attained no more than a year since treatment initiation [107]. Both cyclophosphamide and mycophenolate, combined with glucocorticoids, are indicated as induction therapy. In the largest published cohort including 51 children with proliferative LN followed over a 3-year period, there was no difference between the two treatments in terms of disease activity, urine albumin/creatinine ratio, and serum creatinine [108]. Concerns over cyclophosphamide-related gonadal toxicity and the chronic implications from long-term use of corticosteroids have increased the efforts for alternative regimens with lower cumulative doses; however, there are no long-term efficacy data in children with LN. To this end, limited observational data support the effectiveness of CNIs, multitarget treatment, and biologic agents both in refractory or new-onset disease [109, 110].

Lupus Nephritis During Pregnancy

Lupus affects primarily women of child-bearing age, and therefore, pregnancy is not uncommon throughout the course of the disease. In a large prospective study of 383 pregnant SLE patients, low C4 was associated with renal flares or new-onset LN (OR 5.59; 95% CI 1.64 to 19.13) but not low C3 or positive anti-dsDNA alone [111•]. Patients with active LN are at increased risk for adverse fetal and maternal outcomes [112]. In a recent meta-analysis of four studies including 285 patients, the pooled RR for preterm birth in active LN was 1.78 (95% CI 1.17 to 2.70) compared with counterparts with quiescent disease [113]. Similarly, prospective studies suggest that maternal outcomes such as pre-eclampsia or disease flares are more frequent among women with LN [114, 115]. In line with these findings, the EULAR recommends that the pre-pregnancy counseling and risk assessment should consider both SLE and LN activity [116•]. Inactive/stable disease may permit pre-conception treatment modifications to avoid teratogenic agents such as cyclophosphamide, mycophenolate, methotrexate, and angiotensin-converting enzyme inhibitors. Other agents such as azathioprine, tacrolimus, and cyclosporin are considered safe/acceptable. Finally, there is a consensus regarding the use of hydroxychloroquine in all pregnant women with SLE based on its safety profile and beneficial effects especially on maternal outcomes [117, 118].

Lupus Nephritis During End-Stage Renal Disease

Despite advances, the long-term renal survival in LN has essentially remained unchanged since the 1990s. Interestingly, as LN progresses towards ESRD, disease activity tends to diminish; thus, extra-renal flares are not common post-dialysis [119]. All renal replacement therapies (hemodialysis, peritoneal dialysis, kidney transplantation) can be considered for SLE patients with transplantation demonstrating a

significant survival benefit, and it can be safely performed in quiescent LN patients. Recently, a nationwide cohort study with data from the United States Renal Data System including 20,974 LN-ESRD patients found that transplantation was associated with a 70% reduction in all-cause mortality (hazard ratio 0.30; 95% CI 0.27 to 0.33) [120]. Finally, regarding renal graft survival, most studies have found comparable rates between LN and control recipients [121, 122].

The Cardiovascular Burden of Lupus Nephritis

Patients with SLE have an increased risk of cardiovascular events owing both to traditional and disease-specific risk factors [123]. LN is particularly associated with an additional (2.8- to 8.5-fold) cardiovascular risk compared with non-renal lupus [124–126]. Thus, in a Danish population-based cohort study with 1644 SLE patients, LN patients had significantly increased cardiovascular mortality compared with other SLE patients (HR 8.5, 95% CI 2.2 to 33) [126]. In another retrospective study, Sun et al. [127] performed a class-specific analysis and found a trend for excessive cardiovascular risk associated with proliferative LN. The heightened cardiovascular burden in LN may in part be attributed to the presence of chronic kidney disease and increased prevalence of traditional atherosclerotic risk factors (hypertension, dyslipidemia) and exposure to glucocorticoids. Accordingly, a multifaceted approach is mandated for primary prevention [123], although specific recommendations are still missing.

Conclusions

Despite its lower frequency compared with other manifestations, LN is a serious complication of SLE associated with the need for prolonged intake of glucocorticoids and immunosuppressive or cytotoxic drugs, and increased risk for several comorbidities. A low threshold is required for the early detection of kidney involvement in patients with established SLE, as much as for the diagnosis of SLE in patients who present with abnormal renal function tests; to facilitate the latter, the recent classification criteria for SLE have included high-sensitivity algorithms for classifying LN. In both scenarios, a diagnostic kidney biopsy should be performed promptly, since delay in initiation of immunosuppressive treatment may incur renal damage. First-line treatment with either low-dose intravenous cyclophosphamide or mycophenolate, followed by long-term maintenance immunosuppression, is effective in the majority of cases; however, a considerable proportion of patients will demonstrate delayed or inadequate improvement, accrual of kidney fibrosis, progression into chronic kidney disease, or even ESRD. To expedite or augment the renal response, novel multitarget approaches based on the combination of mycophenolate with either CNI or belimumab have yielded promising results, although it remains unclear whether their added benefit justifies their universal use as induction regimens in LN. Nonetheless, these combinatory regimens together with B cell depleting agents certainly represent useful alternatives in refractory or relapsing disease. Notably, the identification of specific thresholds of proteinuria associated with favorable long-term renal prognosis paves the way for implementing a treat-to-target strategy in LN. Depending on the depth and duration of renal response, gradual tapering of treatment (glucocorticoids first) can be attempted in some cases, and recent evidence suggests that patient selection may be aided by the findings of repeat kidney biopsy.

Notwithstanding the aforementioned advances, several unmet needs exist such as the need for individualized therapeutic decisions based on the clinical presentation, histological findings, and overall SLE status. The evidence base for the management of recalcitrant or flaring disease is limited, and thus, controlled studies are eagerly awaited. In this context, the indications for performing repeat kidney biopsy or whether per-protocol biopsies should be performed in patients with LN remain to be determined. For the future, we remain optimistic that ongoing efforts to decipher the cellular and molecular heterogeneity of lupus kidney inflammation and its progression [128–130] will eventually lead to the discovery of accurate biomarkers and targetable pathways pertaining to the underlying pathophysiology.

Funding Information Christina Adamichou was supported by the Foundation for Research in Rheumatology (FOREUM; protocol number: 016BertsiasPrecl) through the Special Research Fund Account (ELKE).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Gergianaki I, Fanouriakis A, Repa A, Tzanakakis M, Adamichou C, Pompieri A, et al. Epidemiology and burden of systemic lupus erythematosus in a Southern European population: data from the community-based lupus registry of Crete. Greece Ann Rheum

Dis. 2017;76(12):1992–2000. https://doi.org/10.1136/annrheumdis-2017-211206.
2. Wang H, Ren YL, Chang J, Gu L, Sun LY. A systematic review and meta-analysis of prevalence of biopsy-proven lupus nephritis. Arch Rheumatol. 2018;33(1):17–25. https://doi.org/10.5606/ArchRheumatol.2017.6127.
3. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford). 2016;55(2):252–62. https://doi.org/10.1093/rheumatology/kev311.
4. Moroni G, Vercelloni PG, Quaglini S, Gatto M, Gianfreda D, Sacchi L, et al. Changing patterns in clinical-histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis. Ann Rheum Dis. 2018;77(9):1318–25. https://doi.org/10.1136/annrheumdis-2017-212732.
5. Shao SJ, Hou JH, Xie GT, Sun W, Liang DD, Zeng CH, et al. Improvement of outcomes in patients with lupus nephritis: management evolution in Chinese patients from 1994 to 2010. J Rheumatol. 2019;46(8):912–9. https://doi.org/10.3899/jrheum.180145.
6. Choi HS, Han KD, Jung JH, Kim CS, Bae EH, Ma SK, et al. The risk of end-stage renal disease in systemic lupus erythematosus: a nationwide population-based study in Korea. Medicine (Baltimore). 2019;98(28):e16420. https://doi.org/10.1097/MD.0000000000016420.
7. Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. Rheumatology (Oxford). 2011;50(8):1424–30. https://doi.org/10.1093/rheumatology/ker101.
8. Mageau A, Timsit JF, Perrozziello A, Ruckly S, Dupuis C, Bouadma L, et al. The burden of chronic kidney disease in systemic lupus erythematosus: a nationwide epidemiologic study. Autoimmun Rev. 2019;18(7):733–7. https://doi.org/10.1016/j.autrev.2019.05.011.
9. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: a systematic review and Bayesian meta-analysis. Arthritis Rheum. 2016;68(6):1432–41. https://doi.org/10.1002/art.39594.
10. Jolly M, Toloza S, Goker B, Clarke AE, Navarra SV, Wallace D, et al. Disease-specific quality of life in patients with lupus nephritis. Lupus. 2018;27(2):257–64. https://doi.org/10.1177/0961203317717082.
11. Bertsias G, Karampli E, Sidiropoulos P, Gergianaki I, Drosos A, Sakkas L, et al. Clinical and financial burden of active lupus in Greece: a nationwide study. Lupus. 2016;25(12):1385–94. https://doi.org/10.1177/0961203316642310.
12. Hermansen ML, Sandholt B, Fuchs A, Sillesen H, Kober L, Kofoed KF, et al. Atherosclerosis and renal disease involvement in patients with systemic lupus erythematosus: a cross-sectional cohort study. Rheumatology (Oxford). 2018;57(11):1964–71. https://doi.org/10.1093/rheumatology/key201.
13. Teh CL, Phui VE, Ling GR, Ngu LS, Wan SA, Tan CH. Causes and predictors of mortality in biopsy-proven lupus nephritis: the Sarawak experience. Clin Kidney J. 2018;11(1):56–61. https://doi.org/10.1093/ckj/sfx063.
14. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant. 2012;27(8):3248–54. https://doi.org/10.1093/ndt/gfs073.
15. Oliveira C, Mariz H, Fernandes G, Costa D, Cavalcante MA, Valente L. Lupus nephritis class IV-global is associated with a higher risk of end-stage renal disease than class IV-segmental. Nephron. 2020;144(3):118–25. https://doi.org/10.1159/000505404.
16. Faurschou M, Dreyer L, Kamper AL, Starklint H, Jacobsen S. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. Arthritis Care Res. 2010;62(6):873–80. https://doi.org/10.1002/acr.20116.
17. Rijnink EC, Teng YKO, Wilhelmus S, Almekinders M, Wolterbeek R, Cransberg K, et al. Clinical and histopathologic characteristics associated with renal outcomes in lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):734–43. https://doi.org/10.2215/CJN.10601016.
18. Broder A, Mowrey WB, Khan HN, Jovanovic B, Londono-Jimenez A, Izmirly P, et al. Tubulointerstitial damage predicts end stage renal disease in lupus nephritis with preserved to moderately impaired renal function: a retrospective cohort study. Semin Arthritis Rheum. 2018;47(4):545–51. https://doi.org/10.1016/j.semarthrit.2017.07.007.
19. Obrisca B, Jurubita R, Andronesi A, Sorohan B, Achim C, Bobeica R, et al. Histological predictors of renal outcome in lupus nephritis: the importance of tubulointerstitial lesions and scoring of glomerular lesions. Lupus. 2018;27(9):1455–63. https://doi.org/10.1177/0961203318776109.
20. Li C, Yap DYH, Chan G, Wen YB, Li H, Tang C, et al. Clinical outcomes and clinico-pathological correlations in lupus nephritis with kidney biopsy showing thrombotic microangiopathy. J Rheumatol. 2019;46(11):1478–84. https://doi.org/10.3899/jrheum.180773.
21. Dall'Era M, Levesque V, Solomons N, Truman M, Wofsy D. Identification of clinical and serological factors during induction treatment of lupus nephritis that are associated with renal outcome. Lupus Sci Med. 2015;2(1):e000089. https://doi.org/10.1136/lupus-2015-000089.
22. Esdaile JM, Joseph L, MacKenzie T, Kashgarian M, Hayslett JP. The benefit of early treatment with immunosuppressive agents in lupus nephritis. J Rheumatol. 1994;21(11):2046–51.
23. 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 Rheumatol. 2006;33(8):1563–9.
24. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677–86. https://doi.org/10.1002/art.34473.
25. Pons-Estel GJ, Wojdyla D, McGwin G Jr, Magder LS, Petri MA, Pons-Estel BA. The American College of Rheumatology and the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus in two multiethnic cohorts: a commentary. Lupus. 2014;23(1):3–9. https://doi.org/10.1177/0961203313512883.
26.• Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78(9):1151–9. https://doi.org/10.1136/annrheumdis-2018-214819 **The new classification criteria for SLE enable the detection of SLE including renal-limited form with high sensitivity and specificity.**
27. Pons-Estel GJ, Alarcon GS, McGwin G Jr, Danila MI, Zhang J, Bastian HM, et al. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. Arthritis Rheum. 2009;61(6):830–9. https://doi.org/10.1002/art.24538.
28. Kwon OC, Lee JS, Ghang B, Kim YG, Lee CK, Yoo B, et al. Predicting eventual development of lupus nephritis at the time of diagnosis of systemic lupus erythematosus. Semin Arthritis Rheum. 2018;48(3):462–6. https://doi.org/10.1016/j.semarthrit.2018.02.012.

29. Eggleton P, Ukoumunne OC, Cottrell I, Khan A, Maqsood S, Thornes J, et al. Autoantibodies against C1q as a diagnostic measure of lupus nephritis: systematic review and meta-analysis. J Clin Cell Immunol. 2014;5(2):210. https://doi.org/10.4172/2155-9899.1000210.
30. Picard C, Lega JC, Ranchin B, Cochat P, Cabrera N, Fabien N, et al. Anti-C1q autoantibodies as markers of renal involvement in childhood-onset systemic lupus erythematosus. Pediatr Nephrol. 2017;32(9):1537–45. https://doi.org/10.1007/s00467-017-3646-z.
31. Lanata CM, Nititham J, Taylor KE, Chung SA, Torgerson DG, Seldin MF, et al. Genetic contributions to lupus nephritis in a multi-ethnic cohort of systemic lupus erythematous patients. PLoS One. 2018;13(6):e0199003. https://doi.org/10.1371/journal.pone.0199003.
32.• Reid S, Alexsson A, Frodlund M, Morris D, Sandling JK, Bolin K, et al. High genetic risk score is associated with early disease onset, damage accrual and decreased survival in systemic lupus erythematosus. Ann Rheum Dis. 2020;79(3):363–9. https://doi.org/10.1136/annrheumdis-2019-216227 **A large case-control genetic association study reveals that lupus nephritis is associated with high genetic burden.**
33.• Panousis NI, Bertsias GK, Ongen H, Gergianaki I, Tektonidou MG, Trachana M, et al. Combined genetic and transcriptome analysis of patients with SLE: distinct, targetable signatures for susceptibility and severity. Ann Rheum Dis. 2019;78(8):1079–89. https://doi.org/10.1136/annrheumdis-2018-214379 **A whole blood RNA-sequnecing analysis of SLE patients identifies neutrophil gene signature associated with active nephritis.**
34. Toro-Dominguez D, Martorell-Marugan J, Goldman D, Petri M, Carmona-Saez P, Alarcon-Riquelme ME. Stratification of systemic lupus erythematosus patients into three groups of disease activity progression according to longitudinal gene expression. Arthritis Rheum. 2018;70(12):2025–35. https://doi.org/10.1002/art.40653.
35. Almlof JC, Alexsson A, Imgenberg-Kreuz J, Sylwan L, Backlin C, Leonard D, et al. Novel risk genes for systemic lupus erythematosus predicted by random forest classification. Sci Rep. 2017;7(1):6236. https://doi.org/10.1038/s41598-017-06516-1.
36. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71(11):1771–82. https://doi.org/10.1136/annrheumdis-2012-201940.
37. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64(6):797–808. https://doi.org/10.1002/acr.21664.
38.•• Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 Update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis. 2019;78(6):736–45. https://doi.org/10.1136/annrheumdis-2019-215089 **Updated recommendations for the treatment of SLE including lupus nephritis.**
39. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009;20(5):1103–12. https://doi.org/10.1681/ASN.2008101028.
40. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the euro-lupus nephritis trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002;46(8):2121–31. https://doi.org/10.1002/art.10461.
41.• Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, et al. Immunosuppressive treatment for proliferative lupus nephritis. Cochrane Database Syst Rev. 2018;6:CD002922. https://doi.org/10.1002/14651858.CD002922.pub4 **High-quality systematic review and meta-analysis of available treatments in patients with lupus nephritis.**
42.• Rathi M, Goyal A, Jaryal A, Sharma A, Gupta PK, Ramachandran R, et al. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. Kidney Int. 2016;89(1):235–42. https://doi.org/10.1038/ki.2015.318 **Demonstration of the effectiveness of low-dose intravenous cyclophosphamide in class V lupus nephritis.**
43. Sedhain A, Hada R, Agrawal RK, Bhattarai GR, Baral A. Low dose mycophenolate mofetil versus cyclophosphamide in the induction therapy of lupus nephritis in Nepalese population: a randomized control trial. BMC Nephrol. 2018;19(1):175. https://doi.org/10.1186/s12882-018-0973-7.
44. Hanaoka H, Kiyokawa T, Iida H, Ishimori K, Takakuwa Y, Okazaki T, et al. Comparison of renal response to four different induction therapies in Japanese patients with lupus nephritis class III or IV: a single-centre retrospective study. PLoS One. 2017;12(4):e0175152. https://doi.org/10.1371/journal.pone.0175152.
45. Yap DYH, Tang C, Ma MKM, Mok MMY, Chan GCW, Kwan LPY, et al. Longterm data on disease flares in patients with proliferative lupus nephritis in recent years. J Rheumatol. 2017;44(9):1375–83. https://doi.org/10.3899/jrheum.170226.
46. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010;69(12):2083–9. https://doi.org/10.1136/ard.2010.131995.
47. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon GE, Danieli MG, et al. 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(1):61–4. https://doi.org/10.1136/ard.2008.102533.
48. Sabry A, Abo-Zenah H, Medhat T, Sheashaa H, Mahmoud K, El-Huseini A. A comparative study of two intensified pulse cyclophosphamide remission-inducing regimens for diffuse proliferative lupus nephritis: an Egyptian experience. Int Urol Nephrol. 2009;41(1):153–61. https://doi.org/10.1007/s11255-007-9325-4.
49. Group AT. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. Arthritis Rheum. 2014;66(11):3096–104. https://doi.org/10.1002/art.38790.
50. Goswami RP, Sircar G, Sit H, Ghosh A, Ghosh P. Cyclophosphamide versus mycophenolate versus rituximab in lupus nephritis remission induction: a historical head-to-head comparative study. J Clin Rheumatol. 2019;25(1):28–35. https://doi.org/10.1097/RHU.0000000000000760.
51. Mehra S, Usdadiya JB, Jain VK, Misra DP, Negi VS. Comparing the efficacy of low-dose vs high-dose cyclophosphamide regimen as induction therapy in the treatment of proliferative lupus nephritis: a single center study. Rheumatol Int. 2018;38(4):557–68. https://doi.org/10.1007/s00296-018-3995-3.
52. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum. 2013;65(9):2368–79. https://doi.org/10.1002/art.38037.
53. Hannah J, Casian A, D'Cruz D. Tacrolimus use in lupus nephritis: a systematic review and meta-analysis. Autoimmun Rev. 2016;15(1):93–101. https://doi.org/10.1016/j.autrev.2015.09.006.
54.• Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, To CH, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of

lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016;75(1):30–6. https://doi.org/10.1136/annrheumdis-2014-206456 **Randomized trial showing comparable efficacy of tacrolimus versus mycophenolate in Asian patients with lupus nephritis.**

55. Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med. 2015;162(1):18–26. https://doi.org/10.7326/M14-1030.
56.• Rovin BH, Solomons N, Pendergraft WF 3rd, Dooley MA, Tumlin J, Romero-Diaz J, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int. 2019;95(1):219–31. https://doi.org/10.1016/j.kint.2018.08.025 **Evidence for efficacy of the mycophenolate/voclopsorin combination in active lupus nephritis.**
57. Fernandez Nieto M, Jayne DR. Con: the use of calcineurin inhibitors in the treatment of lupus nephritis. Nephrol Dial Transplant. 2016;31(10):1567–71. https://doi.org/10.1093/ndt/gfw291.
58. Gomez Mendez LM, Cascino MD, Garg J, Katsumoto TR, Brakeman P, Dall'Era M, et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. Clin J Am Soc Nephrol. 2018;13(10):1502–9. https://doi.org/10.2215/CJN.01070118.
59. Md Yusof MY, Shaw D, El-Sherbiny YM, Dunn E, Rawstron AC, Emery P, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Ann Rheum Dis. 2017;76(11):1829–36. https://doi.org/10.1136/annrheumdis-2017-211191.
60. McAdoo S, Masoud S, Bedi R, Cairns T, Lightstone L. P06 ofatumumab for B cell depletion therapy in patients with systemic lupus erythematosus who are intolerant of rituximab. Kidney Int Rep. 2016;1(4):S3. https://doi.org/10.1016/j.ekir.2016.09.012.
61. Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase A, Roth DA, et al. Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus. 2013;22(1):63–72. https://doi.org/10.1177/0961203312465781.
62. Kang S, Fedoriw Y, Brenneman EK, Truong YK, Kikly K, Vilen BJ. BAFF induces tertiary lymphoid structures and positions T cells within the glomeruli during lupus nephritis. J Immunol. 2017;198(7):2602–11. https://doi.org/10.4049/jimmunol.1600281.
63. Binda V, Trezzi B, Del Papa N, Beretta L, Frontini G, Porata G, et al. Belimumab may decrease flare rate and allow glucocorticoid withdrawal in lupus nephritis (including dialysis and transplanted patient). J Nephrol. 2020. https://doi.org/10.1007/s40620-020-00706-3.
64.• Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med. 2020;382(3):211–21. https://doi.org/10.1056/NEJMoa1912196 **Successful phase 3 trial of anifrolumab plus standard-of-care versus standard-of-care alone in active SLE.**
65. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365(20):1886–95. https://doi.org/10.1056/NEJMoa1014460.
66. Fanouriakis A, Bertsias G. Changing paradigms in the treatment of systemic lupus erythematosus. Lupus Sci Med. 2019;6(1):e000310. https://doi.org/10.1136/lupus-2018-000310.
67. Zhang X, Ji L, Yang L, Tang X, Qin W. The effect of calcineurin inhibitors in the induction and maintenance treatment of lupus nephritis: a systematic review and meta-analysis. Int Urol Nephrol. 2016;48(5):731–43. https://doi.org/10.1007/s11255-015-1201-z.
68. Zhang H, Liu Z, Zhou M, Liu Z, Chen J, Xing C, et al. Multitarget therapy for maintenance treatment of lupus nephritis. J Am Soc Nephrol. 2017;28(12):3671–8. https://doi.org/10.1681/ASN.2017030263.
69. Moroni G, Longhi S, Giglio E, Messa P, Ponticelli C. What happens after complete withdrawal of therapy in patients with lupus nephritis. Clin Exp Rheumatol. 2013;31(4 Suppl 78):S75–81.
70.• De Rosa M, Azzato F, Toblli JE, De Rosa G, Fuentes F, Nagaraja HN, et al. A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. Kidney Int. 2018;94(4):788–94. https://doi.org/10.1016/j.kint.2018.05.021 **Repeat kidney biopsy with persistent active lesions despite clinical remission is associated with increased risk for flares during treatment withdrawal.**
71. Malvar A, Alberton V, Lococo B, Ferrari M, Delgado P, Nagaraja HN, et al. Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis. Kidney Int. 2020;97(1):156–62. https://doi.org/10.1016/j.kint.2019.07.018.
72. Tang KT, Tseng CH, Hsieh TY, Chen DY. Induction therapy for membranous lupus nephritis: a systematic review and network meta-analysis. Int J Rheum Dis. 2018;21(6):1163–72. https://doi.org/10.1111/1756-185X.13321.
73. Austin HA 3rd, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol. 2009;20(4):901–11. https://doi.org/10.1681/ASN.2008060665.
74. Chavarot N, Verhelst D, Pardon A, Caudwell V, Mercadal L, Sacchi A, et al. Rituximab alone as induction therapy for membranous lupus nephritis: a multicenter retrospective study. Medicine (Baltimore). 2017;96(27):e7429. https://doi.org/10.1097/MD.0000000000007429.
75. Smolen JS. Treat to target in rheumatology: a historical account on occasion of the 10th anniversary. Rheum Dis Clin N Am. 2019;45(4):477–85. https://doi.org/10.1016/j.rdc.2019.07.001.
76. Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the euro-lupus nephritis cohort. Arthritis Rheum. 2015;67(5):1305–13. https://doi.org/10.1002/art.39026.
77. Davidson JE, Fu Q, Ji B, Rao S, Roth D, Magder LS, et al. Renal remission status and longterm renal survival in patients with lupus nephritis: a retrospective cohort analysis. J Rheumatol. 2018;45(5):671–7. https://doi.org/10.3899/jrheum.161554.
78. Medina-Rosas J, Fung WA, Su J, Touma Z. Effect of complete or partial proteinuria recovery on long-term outcomes of lupus nephritis. Semin Arthritis Rheum. 2018;47(4):557–64. https://doi.org/10.1016/j.semarthrit.2017.07.012.
79.• van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Aringer M, Arnaud L, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Ann Rheum Dis. 2017;76(3):554–61. https://doi.org/10.1136/annrheumdis-2016-209519 **Introduction of the treat-to-target concept in the management of SLE.**
80. Kandane-Rathnayake R, Kent JR, Louthrenoo W, Luo SF, Wu YJ, Lateef A, et al. Longitudinal associations of active renal disease with irreversible organ damage accrual in systemic lupus erythematosus. Lupus. 2019;28(14):1669–77. https://doi.org/10.1177/0961203319887799.
81. Ichinose K, Kitamura M, Sato S, Eguchi M, Okamoto M, Endo Y, et al. Complete renal response at 12 months after induction therapy is associated with renal relapse-free rate in lupus nephritis: a

single-center, retrospective cohort study. Lupus. 2019;28(4):501–9. https://doi.org/10.1177/0961203319829827.
82. Won J, Lee JS, Oh JS, Kim YG, Lee CK, Yoo B, et al. Impact of stringent response in proteinuria on long-term renal outcomes in proliferative lupus nephritis. Lupus. 2019;28(11):1294–301. https://doi.org/10.1177/0961203319876695.
83. Tamirou F, Lauwerys BR, Dall'Era M, Mackay M, Rovin B, Cervera R, et al. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. Lupus Sci Med. 2015;2(1):e000123. https://doi.org/10.1136/lupus-2015-000123.
84. Ugolini-Lopes MR, Seguro LPC, Castro MXF, Daffre D, Lopes AC, Borba EF, et al. Early proteinuria response: a valid real-life situation predictor of long-term lupus renal outcome in an ethnically diverse group with severe biopsy-proven nephritis? Lupus Sci Med. 2017;4(1):e000213. https://doi.org/10.1136/lupus-2017-000213.
85. Hanaoka H, Yamada H, Kiyokawa T, Iida H, Suzuki T, Yamasaki Y, et al. Lack of partial renal response by 12 weeks after induction therapy predicts poor renal response and systemic damage accrual in lupus nephritis class III or IV. Arthritis Res Ther. 2017;19(1):4. https://doi.org/10.1186/s13075-016-1202-z.
86. Rovin BH, Parikh SV, Hebert LA, Chan TM, Mok CC, Ginzler EM, et al. Lupus nephritis: induction therapy in severe lupus nephritis—should MMF be considered the drug of choice? Clin J Am Soc Nephrol. 2013;8(1):147–53. https://doi.org/10.2215/CJN.03290412.
87. Wofsy D, Diamond B, Houssiau FA. Crossing the Atlantic: the euro-lupus nephritis regimen in North America. Arthritis Rheum. 2015;67(5):1144–6. https://doi.org/10.1002/art.39067.
88. Touma Z, Urowitz MB, Ibanez D, Gladman DD. Time to recovery from proteinuria in patients with lupus nephritis receiving standard treatment. J Rheumatol. 2014;41(4):688–97. https://doi.org/10.3899/jrheum.130005.
89. Grootscholten C, Ligtenberg G, Hagen EC, van den Wall Bake AW, de Glas-Vos JW, Bijl M, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int. 2006;70(4):732–42. https://doi.org/10.1038/sj.ki.5001630.
90. Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ, Collaborative SG. Value of a complete or partial remission in severe lupus nephritis. Clin J Am Soc Nephrol. 2008;3(1):46–53. https://doi.org/10.2215/CJN.03280807.
91. Adamichou C, Bertsias A. Flares in systemic lupus erythematosus: diagnosis, risk factors and preventive strategies. Mediterr J Rheumatol. 2017;28(1):4–12. https://doi.org/10.31138/mjr.28.1.4.
92. Parikh SV, Nagaraja HN, Hebert L, Rovin BH. Renal flare as a predictor of incident and progressive CKD in patients with lupus nephritis. Clin J Am Soc Nephrol. 2014;9(2):279–84. https://doi.org/10.2215/CJN.05040513.
93. Mejia-Vilet JM, Cordova-Sanchez BM, Arreola-Guerra JM, Morales-Buenrostro LE, Uribe-Uribe NO, Correa-Rotter R. Renal flare prediction and prognosis in lupus nephritis Hispanic patients. Lupus. 2016;25(3):315–24. https://doi.org/10.1177/0961203315606985.
94. Yap DYH, Kwan LPY, Ma MKM, Mok MMY, Chan GCW, Chan TM. Preemptive immunosuppressive treatment for asymptomatic serological reactivation may reduce renal flares in patients with lupus nephritis: a cohort study. Nephrol Dial Transplant. 2019;34(3):467–73. https://doi.org/10.1093/ndt/gfy024.
95. Narvaez J, Ricse M, Goma M, Mitjavila F, Fulladosa X, Capdevila O, et al. The value of repeat biopsy in lupus nephritis flares. Medicine (Baltimore). 2017;96(24):e7099. https://doi.org/10.1097/MD.0000000000007099.
96. Malvar A, Pirruccio P, Alberton V, Lococo B, Recalde C, Fazini B, et al. Histologic versus clinical remission in proliferative lupus nephritis. Nephrol Dial Transplant. 2017;32(8):1338–44. https://doi.org/10.1093/ndt/gfv296.
97. Zickert A, Sundelin B, Svenungsson E, Gunnarsson I. Role of early repeated renal biopsies in lupus nephritis. Lupus Sci Med. 2014;1(1):e000018. https://doi.org/10.1136/lupus-2014-000018.
98. Pineiro GJ, Arrizabalaga P, Sole M, Abellana RM, Espinosa G, Cervera R. Repeated renal biopsy - a predictive tool to assess the probability of renal flare in lupus nephritis. Am J Nephrol. 2016;44(6):439–46. https://doi.org/10.1159/000452229.
99. Kalloo S, Aggarwal N, Mohan P, Radhakrishnan J. Lupus nephritis: treatment of resistant disease. Clin J Am Soc Nephrol. 2013;8(1):154–61. https://doi.org/10.2215/CJN.05870612.
100. Rivera F, Merida E, Illescas ML, Lopez-Rubio E, Frutos MA, Garcia-Frias P, et al. Mycophenolate in refractory and relapsing lupus nephritis. Am J Nephrol. 2014;40(2):105–12. https://doi.org/10.1159/000365256.
101. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol. 2008;19(10):2001–10. https://doi.org/10.1681/ASN.2007121272.
102. Jesus D, Rodrigues M, da Silva JAP, Ines L. Multitarget therapy of mycophenolate mofetil and cyclosporine a for induction treatment of refractory lupus nephritis. Lupus. 2018;27(8):1358–62. https://doi.org/10.1177/0961203318758508.
103. Alshaiki F, Obaid E, Almuallim A, Taha R, El-Haddad H, Almoallim H. Outcomes of rituximab therapy in refractory lupus: a meta-analysis. Eur J Rheumatol. 2018;5(2):118–26. https://doi.org/10.5152/eurjrheum.2018.17096.
104. Anutrakulchai S, Panaput T, Wongchinsri J, Chaishayanon S, Satirapoj B, Traitanon O, et al. A multicentre, randomised controlled study of enteric-coated mycophenolate sodium for the treatment of relapsed or resistant proliferative lupus nephritis: an Asian experience. Lupus Sci Med. 2016;3(1):e000120. https://doi.org/10.1136/lupus-2015-000120.
105. Choi CB, Won S, Bae SC. Outcomes of multitarget therapy using mycophenolate mofetil and tacrolimus for refractory or relapsing lupus nephritis. Lupus. 2018;27(6):1007–11. https://doi.org/10.1177/0961203318758505.
106. Moroni G, Gallelli B, Sinico RA, Romano G, Sinigaglia L, Messa P. Rituximab versus oral cyclophosphamide for treatment of relapses of proliferative lupus nephritis: a clinical observational study. Ann Rheum Dis. 2012;71(10):1751–2. https://doi.org/10.1136/annrheumdis-2012-201442.
107. Groot N, de Graeff N, Marks SD, Brogan P, Avcin T, Bader-Meunier B, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. Ann Rheum Dis. 2017;76(12):1965–73. https://doi.org/10.1136/annrheumdis-2017-211898.
108. Smith E, Al-Abadi E, Armon K, Bailey K, Ciurtin C, Davidson J, et al. Outcomes following mycophenolate mofetil versus cyclophosphamide induction treatment for proliferative juvenile-onset lupus nephritis. Lupus. 2019;28(5):613–20. https://doi.org/10.1177/0961203319836712.
109. Basu B, Roy B, Babu BG. Efficacy and safety of rituximab in comparison with common induction therapies in pediatric active lupus nephritis. Pediatr Nephrol. 2017;32(6):1013–21. https://doi.org/10.1007/s00467-017-3583-x.
110. Aragon E, Resontoc LP, Chan YH, Lau YW, Tan PH, Loh HL, et al. Long-term outcomes with multi-targeted immunosuppressive protocol in children with severe proliferative lupus nephritis. Lupus. 2016;25(4):399–406. https://doi.org/10.1177/0961203315615220.
111.• Buyon JP, Kim MY, Guerra MM, Lu S, Reeves E, Petri M, et al. Kidney outcomes and risk factors for nephritis (flare/de novo) in a

multiethnic cohort of pregnant patients with lupus. Clin J Am Soc Nephrol. 2017;12(6):940–6. https://doi.org/10.2215/CJN.11431116 **Prospective evaluation of a large cohort of pregnant SLE women for the indetificatio of risk factors associated with flaring or new-onset nephritis.**

112. Attia DH, Mokbel A, Haggag HM, Naeem N. Pregnancy outcome in women with active and inactive lupus nephritis: a prospective cohort study. Lupus. 2019;28(7):806–17. https://doi.org/10.1177/0961203319846650.
113. Wei S, Lai K, Yang Z, Zeng K. Systemic lupus erythematosus and risk of preterm birth: a systematic review and meta-analysis of observational studies. Lupus. 2017;26(6):563–71. https://doi.org/10.1177/0961203316686704.
114. Rodrigues BC, Lacerda MI, Ramires de Jesus GR, Cunha Dos Santos F, Ramires de Jesus N, Levy RA, et al. The impact of different classes of lupus nephritis on maternal and fetal outcomes: a cohort study of 147 pregnancies. Lupus. 2019;28(4):492–500. https://doi.org/10.1177/0961203319829825.
115. Moroni G, Doria A, Giglio E, Imbasciati E, Tani C, Zen M, et al. Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study. J Autoimmun. 2016;74:194–200. https://doi.org/10.1016/j.jaut.2016.06.012.
116.• Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis. 2017;76(3):476–85. https://doi.org/10.1136/annrheumdis-2016-209770 **The EULAR recommendations for risk stratification and use of safe treatments during pregnancy in women with SLE including lupus nephritis.**
117. Sperber K, Hom C, Chao CP, Shapiro D, Ash J. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. Pediatr Rheumatol Online J. 2009;7:9. https://doi.org/10.1186/1546-0096-7-9.
118. Seo MR, Chae J, Kim YM, Cha HS, Choi SJ, Oh S, et al. Hydroxychloroquine treatment during pregnancy in lupus patients is associated with lower risk of preeclampsia. Lupus. 2019;28(6):722–30. https://doi.org/10.1177/0961203319843343.
119. Mattos P, Santiago MB. Disease activity in systemic lupus erythematosus patients with end-stage renal disease: systematic review of the literature. Clin Rheumatol. 2012;31(6):897–905. https://doi.org/10.1007/s10067-012-1957-9.
120. Jorge A, Wallace ZS, Lu N, Zhang Y, Choi HK. Renal transplantation and survival among patients with lupus nephritis: a cohort study. Ann Intern Med. 2019;170(4):240–7. https://doi.org/10.7326/M18-1570.
121. Naranjo-Escobar J, Manzi E, Posada JG, Mesa L, Echeverri GJ, Duran C, et al. Kidney transplantation for end-stage renal disease in lupus nephritis, a very safe procedure: a single Latin American transplant center experience. Lupus. 2017;26(11):1157–65. https://doi.org/10.1177/0961203317696591.
122. Kim JE, Kim YC, Min SL, Lee H, Ha J, Chin HJ, et al. Transplant outcomes in kidney recipients with lupus nephritis, and systematic review. Lupus. 2020;29(3):248–55. 961203320902524. https://doi.org/10.1177/0961203320902524.
123. Kostopoulou M, Nikolopoulos D, Parodis I, Bertsias G. Cardiovascular disease in systemic lupus erythematosus: recent data on epidemiology, risk factors and prevention. Curr Vasc Pharmacol. 2019. https://doi.org/10.2174/1570161118666191227101636.
124. Wells DK, Ward MM. Nephritis and the risk of acute myocardial infarction in patients with systemic lupus erythematosus. Clin Exp Rheumatol. 2010;28(2):223–9.
125. Reppe Moe SE, Molberg O, Strom EH, Lerang K. Assessing the relative impact of lupus nephritis on mortality in a population-based systemic lupus erythematosus cohort. Lupus. 2019;28(7):818–25. https://doi.org/10.1177/0961203319847275.
126. Hermansen ML, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. The risk of cardiovascular morbidity and cardiovascular mortality in systemic lupus erythematosus and lupus nephritis: a Danish nationwide population-based cohort study. Rheumatology (Oxford). 2017;56(5):709–15. https://doi.org/10.1093/rheumatology/kew475.
127. Sun EY, Alvarez C, Sheikh SZ. Association of lupus nephritis with coronary artery disease by ISN/RPS classification: results from a large real-world lupus population. ACR Open Rheumatol. 2019;1(4):244–50. https://doi.org/10.1002/acr2.1035.
128.• Arazi A, Rao DA, Berthier CC, Davidson A, Liu Y, Hoover PJ, et al. The immune cell landscape in kidneys of patients with lupus nephritis. Nat Immunol. 2019;20(7):902–14. https://doi.org/10.1038/s41590-019-0398-x **Single-cell transcriptome analysis of kidney tissue from patients with lupus nephritis.**
129.• Der E, Ranabothu S, Suryawanshi H, Akat KM, Clancy R, Morozov P, et al. Single cell RNA sequencing to dissect the molecular heterogeneity in lupus nephritis. JCI Insight. 2017;2(9):e93009. https://doi.org/10.1172/jci.insight.93009 **Single-cell transcriptome analysis of kidney tissue from patients with lupus nephritis.**
130. Pamfil C, Makowska Z, De Groof A, Tilman G, Babaei S, Galant C, et al. Intrarenal activation of adaptive immune effectors is associated with tubular damage and impaired renal function in lupus nephritis. Ann Rheum Dis. 2018;77(12):1782–9. https://doi.org/10.1136/annrheumdis-2018-213485.