REVIEW

A Review of Lupus Nephritis

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Background: Lupus nephritis (LN) is one of the most common severe organ manifestations of systemic lupus erythematosus (SLE). LN is associated with significant morbidity and mortality in SLE patients, as up to 20% of patients progress to end-stage renal disease (ESRD). The clinical manifestations of LN are variable, ranging from asymptomatic proteinuria to a myriad of manifestations associated with nephritic and nephrotic syndromes and ESRD. It is therefore important to screen all SLE patients for LN.

Content: Urinalysis is a useful screening test in LN. Quantification of proteinuria can be performed with either a urine protein-to-creatinine ratio or 24-h urine sample collection for protein. Renal biopsy remains the gold standard for diagnosis of LN. Traditional serum biomarkers used to monitor SLE and LN disease activity and flares include anti–double-stranded DNA antibodies and complement components 3 and 4. Other nonconventional biomarkers found to correlate with LN include anti-C1q and surrogate markers of type 1 interferon regulatory genes (INF gene signature). Potential urinary biomarkers for LN include monocyte chemoattractant protein 1, neutrophil gelatinase-associated lipocalin, tumor necrosis factor-like inducer of apoptosis, and vascular cell adhesion molecule 1.

Summary: Although studies have shown promising results for the use of alternative biomarkers, these require validation in prospective studies to support their use. Renal remission rates in patients receiving standard of care therapy for induction and maintenance treatment of LN remain low. This has prompted further research in newer therapeutic targets in LN ,which have shown promising results.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease most common in females of childbearing age and postmenopausal women (1). SLE is characterized by a heterogeneous clinical presentation. Lupus nephritis (LN) is a form of glomerulonephritis that can occur in patients with SLE, and it is one the most common and severe organ manifestation of SLE, affecting more than 50% of patients. Often, LN occurs within the first 5 years of SLE diagnosis (2–4).

The American College of Rheumatology defines LN based on the presence of persistent proteinuria >0.5 g/24 h or >3 by urine dipstick or presence of cellular casts, including red blood cells and hemoglobin (granular, tubular, or mixed) (5, 6). The 2012 Systemic Lupus International Collaborating Clinics classification criteria defined renal involvement as a urinary protein-to-creatinine ratio (PCR)

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IMPACT STATEMENT

In this review, we highlight the importance of screening for lupus nephritis (LN). Early diagnosis and management of LN is essential, as it can reduce morbidity and mortality. We also summarize the incidence and prevalence of LN, diagnostic tests including nonconventional urinary and serum biomarkers, and the recommended management. We also discuss more recent studies that have shown benefit of newer therapeutic targets in the management of LN, which will likely influence the recommended management in the near future.

or 24 h urinary protein excretion corresponding to 0.5 g daily or the presence of red blood cell casts in urinary sediment (7). In the presence of clinical and laboratory evidence of LN, a renal biopsy should be performed to confirm the diagnosis (5).

Clinical manifestations of LN vary from asymptomatic proteinuria to overt nephrotic syndrome, and can lead to end-stage renal disease (ESRD) (2, 4). LN is one of the most common causes of death, as well as an important predictor of subsequent mortality in SLE (2, 8–12). It is also associated with a significant morbidity, since up to 20% of patients will progress to ESRD (2, 13), which has a particularly high socioeconomic impact, since the great majority are younger than 50 years (14, 15).

Despite current immunosuppressive therapy, renal remission following treatment with first-line immunosuppression remains low, and for those who respond, 35% will experience at least one relapse (16, 17). Recent studies have shown a trend toward less chronic histologic changes over the last decades in newly diagnosed LN patients (2, 18), which, in turn, was associated with a decrease in ESRD, highlighting the importance of early diagnosis and treatment of LN in preventing irreversible renal damage.

It is therefore important to constantly screen all SLE patients for LN early. Renal biopsy remains the gold standard test for diagnosing LN and classifying activity and chronicity (19, 20).

Current traditional biomarkers that are used to diagnose and monitor LN activity, although readily available, cannot reliably predict LN (21, 22). Several novel serum and urinary biomarkers have been identified that correlate with LN activity (23–26). Although these novel biomarkers are not routinely used in current clinical practice, there is expanding research on this topic, which may lead to their use in routine clinical practice in the near future.

As for the management of LN, despite improvement in the morbidity and mortality of patients with LN, the rates of flare remain high, and the remission rates are low even with optimal management (27–29). Currently, mycophenolate (MMF) particularly, as well as cyclophosphamide (CYC), combined with high-dose prednisone are the standard of care for induction therapy. MMF is more widely used as the first-line treatment for induction therapy, as it has been shown to have fewer adverse events in the short and long term compared to CYC (30). In patients who do not respond to treatment with MMF and CYC, other immunosuppressants are used (5). As for maintenance therapy, immunosuppression with azathioprine or MMF is recommended. Over the last 2 years, new drugs for LN have been approved, and this will have an implication for the future management LN.

Studies have revealed that the time for renal recovery can be slow. A study that assessed the time to recovery from proteinuria in patients with LN showed that 28% of patients who receive standard-of-care therapy had complete recovery (proteinuria <0.5 g/day) after the first 12 months, 52% by 2 years, and 74% by 5 years (31).

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In this review, we provide an overview of LN, discussing epidemiology; classification of LN; clinical manifestations and diagnosis, including conventional and nonconventional serum and urinary biomarkers; and management.

EPIDEMIOLOGY

In the United States, the estimated incidence of SLE ranges widely, from 3.7 per 100 000 person-years to 49 per 100 000 person-years (32, 33). The annual incidence has been found to be higher in Black patients compared to White patients in Michigan (7.9 vs 3.7 per 100 000 person-years) and Georgia (9.4 vs 3.2 per 100 000 person-years) (34, 35). There is also higher reported incidence for LN in American Indians/Alaska Natives (7.4 per 100 000 person-years). In San Francisco County and Manhattan, incidence is 4.1 and 4.0 per 100 000 person-years, respectively, for Hispanics and 4.2 and 3.8 per 100 000 person-years, respectively, for Asians (36, 37). Recent epidemiologic data on the prevalence of SLE in the United States revealed an overall prevalence of 72.8 per 100 000 person-years. The prevalence was 9 times higher among females than males (38).

In Canada, data from Alberta revealed an overall incidence of SLE for all age groups of 4.43 per 100 000 person-years. The prevalence of SLE was found to increase over time, as in the year 2000, the prevalence was 47.99 per 100 000 person-years, which increased to 90 per 100 000 person-years by 2015 (39).

SLE is more prevalent in females, with a female to male ratio of 3:1 to 15:1. In children, for whom the influence of sex hormones is presumed to be minimal, the ratio is 3:1, and in women of childbearing age, the ratio ranges from 9:1 to 15:1 (40, 41). The higher female prevalence has partially been attributed to estrogen hormone effect, as well as other sex hormones such as prolactin, dehydroepiandrosterone, and testosterone (42). Another proposed cause for the high prevalence of SLE in female is that the double X chromosomes increase the chance of TLR7 on chromosome X escaping inactivation in the innate immune system, binding single-stranded RNA and activating type 1 interferon (IFN) signaling. This pathway is important in SLE patients (43, 44).

In patients with SLE, 25% to 50% will have LN at time of diagnosis, but the overall prevalence of LN in patients with SLE can reach 50% to 65% throughout the disease course (45).

Risk factors associated with poor prognosis in patients with LN include African-American race, Hispanic ethnicity, male sex, older age, and inadequate response to conventional therapy. Intrinsic renal factors associated with poor prognosis include the International Society of Nephrology/Renal Pathology Society (ISN/RPS) proliferative classes (18), with class IV being associated with an increased risk of up to 44% for the development of ESRD (14). Even though the prognosis of class V is generally favorable, African cohorts have reported poorer outcomes compared to Asian and European cohorts (46). Increased serum creatinine, interstitial inflammation, and interstitial fibrosis are other factors associated with poor prognosis (47).

LUPUS NEPHRITIS

Clinical Manifestations and Diagnosis

Urinary studies. The clinical manifestations of LN are variable, ranging from asymptomatic proteinuria to overt proteinuria, nephrotic syndrome or nephritic syndrome, and ESRD. Rarely, patients can present with "silent" LN, where patients do not have any findings of clinical renal disease but have histologic changes on renal biopsy consistent with LN (48, 49).

A study that assessed the frequency of significant LN on biopsy in SLE patients with silent LN

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revealed that 62% had class I or II LN, 15% had class III or IV LN, and 10% had class V LN. The remaining 13% of patients had no evidence of LN on biopsy (49).

Initially, urinalysis can be performed as it is a useful screening tool for LN. In patients with LN who do present with clinical renal disease, proteinuria is found in 100% of patients with LN, and nephrotic range proteinuria is found in 50% of all patients with LN. Other abnormalities seen on urinalysis in patients with LN are microscopic hematuria, granular casts, cellular casts, and macroscopic hematuria (50–52). If the urinalysis is abnormal and proteinuria is suspected, quantification of proteinuria can be performed with either urine PCR or 24-h urine sample collection for protein (24H-P).

PCR is convenient, as quantification of proteinuria is performed on a single voided urine sample. This can be inaccurate if the level of protein excretion is variable during a 24-h period. In patients with an abnormal PCR, a 24H-P should be performed for more accurate quantification of the degree of proteinuria (19, 20, 53, 54). Several studies have revealed poor reliability of urinalysis and 24 h urine PCR in diagnosing and predicting the degree of LN (50, 51, 55, 56). These are therefore helpful screening tools in all patients with SLE but highlight the importance of early renal biopsy when clinically indicated, particularly when proteinuria is ≥ 0.5 g/24 h (51, 54).

Renal biopsy. Renal biopsy remains the gold standard for the diagnosis of LN when proteinuria is identified. Renal biopsy provides information on the degree of inflammation, the extent of damage, and rules out other causes of proteinuria or renal dysfunction in patients with SLE such as IgA nephropathy, antiphospholipid antibody-associated nephropathy, hypertensive nephrosclerosis, thin basement membrane disease, and others (5, 51, 55). The clinical and pathological spectrum of LN is heterogeneous and therefore it is also important to rule out other pathology that may be seen in lupus, such as thrombotic microangiopathy (57).

Although there are varying opinions on the criteria for renal biopsy, several studies and guidelines have suggested renal biopsy in patients with proteinuria > 0.5 g/24 h in the absence of renal failure can still be associated with significant renal inflammation (51, 58). Renal biopsy is therefore recommended for patients with SLE with hematuria and/or cellular casts, proteinuria >0.5 g/24 h (or urinary PCR > 500 mg/g), or unexplained decrease in glomerular filtration rate (GFR) (51).

Histopathologic classification of LN. The initial classification of glomerular changes in LN was described in 1974 by the World Health Organization (WHO). Glomerular changes were divided into 5 classes: class I, where no detectable changes are seen in the glomeruli; class II, for pure mesangial disease; class III, defined as proliferative disease affecting <50% of the glomeruli; class IV, proliferative disease affecting >50% of the glomeruli; and class V, for membranous changes. In 1982, this was modified, and an additional category class VI was introduced, which was for advanced sclerosing glomerulonephritis (59).

In 2003, the ISN/RPS system proposed new classification criteria (i.e., 6 classes), but the main change was subdivision of class IV into diffuse segmental or diffuse global and introduction of the terms *active*, *chronic*, and *acute-on-chronic* lesions (59). This remains the currently accepted classification criteria and is summarized in Table 1.

The ISN/RPS classification was revised in 2018, and it attempts to account for both glomerular and tubulointerstitial lesions (60). This revision has not been approved by the ISN/RPS yet. The 2003 ISN/RPS classification continues to be the currently accepted classification.

Serum Biomarkers

Traditional biomarkers. The production of autoantibodies is one of the hallmarks of SLE, and therefore autoantibodies are useful biomarkers

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Table 1. 2003 ISN/RPS histopathologic classification.

Class	Definition	Description
I	Minimal mesangial LN	Normal glomeruli by LM,[a] but mesangial immune deposits on IF[b] or EM.[c]
II	Mesangial proliferative LN	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by LM, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by IF or EM, but not by LM.
III	Focal LN	Active or inactive focal, segmental or global endocapillary or extra-capillary glomerulonephritis involving <50% of all glomeruli:
		III (A)[d]: Active lesions
		III (A/C)[e]: Active and chronic lesions
		III (C)[f]: Chronic inactive lesions
IV	Diffuse LN	Active or inactive diffuse, S[g] or G[h] endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli:
		IV-S: ≥50% glomeruli with segmental lesions
		IV-G: ≥50% glomeruli with global lesions
		IV-S(A), IV-G(A): active lesions
		IV-S(A/C), IV-G(A/C): active and chronic lesions
		IV-S(C), IV-G(C): chronic inactive lesions
V	Membranous LN	G or S subepithelial immune deposits or their morphological sequelae by LM and by IF or EM, with or without mesangial alterations. May occur in combination with class III or IV, in which case both classes are diagnosed. May show advanced sclerosis.
VI	Advanced sclerotic LN	≥90% of glomeruli globally sclerosed without residual activity.

[a]Light microscopy.
[b]Immunofluorescence.
[c]Electron microscopy.
[d]Acute.
[e]Acute-on-chronic.
[f]Chronic.
[g]Segmental.
[h]Global.
Adapted from Parikh et al. (155).

in the diagnosis and monitoring of lupus. Autoantibodies to double-stranded DNA (dsDNA) and markers of complement activation (C3, C4) are widely used in the diagnosis and surveillance of patients with SLE and LN (1). Several studies have demonstrated that high titers of anti-dsDNA antibodies and low C3 and C4 levels precede a LN flare (4, 8). However, not all patients with high titers of anti-dsDNA antibodies develop nephritis (21); similarly, changes in complement levels have yielded variable results to predict a kidney flare (22) or response to therapy. Overall, these biomarkers have low sensitivity and specificity for LN flares (21).

Other autoantibodies. C1q is the first component of the classic complement system and plays an important role in the clearance of immune complexes and apoptotic bodies (61). Multiple studies have found a correlation between autoantibodies to C1q and the presence of LN (21, 62–64). Furthermore, a possible predictive value has been suggested. The study by Coremans et al. found that anti C1q antibodies predicted renal activity 3 to 6 months prior to the flare (65). In addition, the study by Yang et al. reported that the combination of anti-C1q and anti-dsDNA antibodies predicted poor renal outcomes in a cohort

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of patients who were followed for 5 years (66). Even though there is evidence suggesting the utility of anti-C1q antibodies for the surveillance of LN when compared to the traditional anti-dsDNA antibodies, anti-C1q antibodies have not proven to be superior but may nonetheless provide useful additional information (62, 63, 66). Whether these autoantibodies will be used in a clinical setting still requires further investigation. Antinucleosome antibodies appear earlier during the disease course when compared to anti-dsDNA autoantibodies (67) and correlate with disease activity and LN (67, 68); thus, they may be helpful in SLE of recent onset, especially when anti-dsDNA antibodies are negative.

Type I interferon. Genome-wide expression studies have highlighted that most patients with SLE have increased expression of IFN-I regulatory genes, known as the IFN gene signature, seen in over 85% of children and 70% of adults with SLE (69, 70). It has become appreciated that IFN-I plays a central role in the pathogenesis of SLE (71, 72), and in recent years, accumulating data support the concept that activation of the IFN-I pathway in SLE is associated not only with disease pathogenesis but also disease severity. In cross-sectional studies, increased IFN-I regulatory gene levels in peripheral blood mononuclear cells and high serum IFN-I activity are associated with disease activity, including higher SLE Disease Activity Index scores and the presence of renal involvement (73, 74). Furthermore, we and others have demonstrated that a high baseline of IFN-I regulatory genes predicts risk of flare and a more severe disease course with an increased mean disease activity and requirement for more aggressive therapy (75, 76). A recent study that measured IFN-I through serum IFN-α levels found that high levels of serum IFN-α identified patients with a high risk of relapse in a clinical quiescent lupus cohort (77). Taken together, these results suggest that the levels of IFN-I may help detect patients who are at risk of a more severe disease course.

Specifically referring to kidney involvement, transcriptomic studies performed on renal biopsies from proliferative LN patients showed that patients who were refractory to conventional therapy had a higher IFN-I signature on their renal tubular cells (78, 79). However, this finding still needs external validation.

Given that gene expression is not yet applicable in routine clinical settings, surrogate markers of IFN-I signature have been studied, including C-X-C motif chemokine ligand 10, galectin-9, and sialic acid–binding Ig-like lectin 1 (80, 81). C-X-C motif chemokine ligand 10 has the strongest correlation with SLE disease activity and renal flares (80). Interleukin (IL)-1 family, specifically IL-18 cytokine, is a major inducer of type II IFN and has been studied as a biomarker for SLE disease activity; in addition, active LN has been found to be associated with high IL-18 levels (81). Types I and II IFN also regulate the expression and secretion of B-cell activating factor (BAFF), which is key to B-cell development. BAFF levels in SLE have found to increase with serological activity and can predict disease flares. Furthermore, higher expression of BAFF in kidney biopsies is found in proliferative classes and correlates with the histopathological disease activity index (82, 83). None of these potential biomarkers are available in the clinical setting, as further validation studies are warranted.

Urinary Biomarkers

Given the lack of noninvasive biomarkers that can be used to accurately predict response to treatment and renal outcomes, there has been tremendous interest in the development of novel LN biomarkers. Urine is easily obtained and may be more promising when compared to serum biomarkers as they may specifically reflect kidney inflammation.

In addition to its diagnostic utility, proteinuria is used to determine response to treatment and predict renal outcomes. Several studies have shown that the levels of proteinuria at 1 year

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following treatment is a good predictor of long-term renal survival (84–86). However, its utility as a biomarker has drawbacks as LN-associated proteinuria frequently persists for years after renal injury, especially in patients with nephrotic range proteinuria, normalizing in <50% of patients within 2 years (31). Furthermore, proteinuria can reflect chronic histologic lesions rather than active inflammation within the kidney, as Malvar et al. have demonstrated, where 62% of the LN patients who had complete histologic remission on a repeat renal biopsy following induction therapy were still "clinically active," characterized by persistent proteinuria (87). This last point is a challenge for clinicians, as being able to differentiate between residual activity and damage in LN is crucial when treating patients.

Various urinary cytokines, chemokines, proinflammatory factors, growth factors, and adhesion molecules have been assessed as potential urinary biomarkers for LN. Some of them have been shown to correlate with the degree of activity in the kidney biopsy, while others are more associated with chronicity and renal reserve.

Monocyte chemoattractant protein 1 (MCP1) was found to correctly differentiate between active LN and non-LN (88–90) and to correlate strongly with the histopathologic activity index (88). In one study, it outperformed traditional serologic markers (C3, C4, and dsDNA antibodies) in differentiating active LN (91). In addition, a longitudinal cohort reported that MCP1 increased 2 to 4 months prior to a renal flare (92). A predictive role for this biomarker has been suggested, as higher baseline levels have correlated with impaired renal function and poor clinical outcomes (91, 93, 94).

Adiponectin has correlated in cross sectional studies with the presence of active nephritis, the activity index (88, 95), and the degree of proteinuria (96). Furthermore, in a longitudinal cohort, it was found to increase 2 months prior to the LN flare (95), and in an independent pediatric lupus cohort, adiponectin anticipated treatment response (area under the ROC curve > 0.9) as early as month 3 (97).

Neutrophil gelatinase–associated lipocalin has been studied extensively over the last 2 decades in acute kidney injury and LN. A recent metanalysis (98) concluded that urinary neutrophil gelatinase–associated lipocalin was useful in the diagnosis of LN, with a pooled sensitivity and specificity of 0.87 and 0.82, respectively. It was also useful for estimating histologic activity and predicting renal flare of LN, although this last point was based on a single study (99). Its utility in distinguishing proliferative LN was limited due to the low number of studies (98).

Tumor necrosis factor–like weak inducer of apoptosis (TWEAK) is a proinflammatory cytokine, a member of the tumor necrosis factor family. Studies suggest that TWEAK may play a role in the pathogenesis of LN as TWEAK activation augments kidney damage (100, 101) and its inhibition can attenuate renal damage in murine lupus models (102, 103). Several studies, mostly cross-sectional, have reported higher urinary TWEAK levels in patients with active LN vs those without (104–107); in one study, TWEAK levels even outperformed complement and anti-dsDNA levels (13). Its correlation with the activity index in kidney biopsies is contradictory between studies (24, 107, 108). In a more recent publication, it was found to predict response to therapy, even though it did not outperform proteinuria; the study suggests that the combination of urinary TWEAK and proteinuria at 3 months after flare could improve the predictive performance for complete response at 6 months (24).

BAFF and proliferation-inducing ligand (APRIL) have been associated with overall lupus activity (109). In addition, BAFF expression in renal tubular cells has been found in patients with proliferative LN, correlating with the activity index (83). Urinary levels of BAFF and APRIL are also detected and increased in active LN, outperforming complement and dsDNA antibodies (25).

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There are also many adhesion molecules described that correlate with LN. These include vascular cell adhesion molecule 1 and activated leucocyte cell adhesion molecule. Both urinary soluble vascular cell adhesion molecule 1 and soluble activated leucocyte cell adhesion molecule have been able to distinguish SLE patients with active LN from patients with quiescent or no prior nephritis (26, 88, 110). Furthermore, high soluble vascular cell adhesion molecule 1 levels have been found to increase the risk of poor renal outcomes (26).

Increased kidney expression of matrix metalloproteinases (MMP) has been found in the glomeruli of LN patients, correlating with the activity index and kidney function (111). A recent study reported that urinary MMP7 levels were significantly higher in patients with active LN vs those with active extrarenal lupus, non-SLE glomerular diseases, or healthy controls. In addition, MMP7 correlated with the histologic activity index and outperformed conventional serologic markers and proteinuria. Furthermore, the authors validated their results in a longitudinal cohort, finding that the urinary MMP7 levels increased prior to the LN flare, occurring earlier than proteinuria (112).

In pediatric SLE, a panel of 6 urinary biomarkers named RAIL (neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein-1, ceruloplasmin, adiponectin, hemopexin, and KIM-1) correlated with histologic renal activity with an area under the ROC curve of 0.92 (113). This biomarker panel was further validated in an adult cohort, demonstrating the role of RAIL in predicting LN activity (114). The same panel was assessed in a longitudinal cohort, demonstrating accuracy at month 3 (area under the ROC curve 0.92) to anticipate response to therapy (97), although RAIL did not outperform the GFR to predict chronic LN damage (115).

Epidermal growth factor is detectable in the urine of normal healthy individuals and has been reported to be decreased in several kidney diseases (116). Although not specific to LN (116–118), in a recent study, urinary epidermal growth factor levels correlated with histologic kidney damage in patients with LN. Furthermore, low urinary epidermal growth factor levels at the time of the renal flare and decreasing levels over time correlated with adverse long-term kidney outcomes (119).

As outlined, the study of urinary biomarkers started over 2 decades ago, and although promising data have been reported, none of these biomarkers are currently used in clinical practice for LN. Their adoption in the clinical settings is challenged by the fact that the great majority of the studies are performed in single centers without external validation, most are cross-sectional studies, and the methods of quantification and cutoffs values differ from study to study. A homogenization of studies designs may help the future of novel urinary biomarkers.

Management

The goal in the treatment of LN is the resolution of active inflammation and to achieve a state of renal remission and disease quiescence. Immunosuppressive therapy is used for proliferative forms of LN such as classes III, IV, or class III/IV with class V LN. Treatment with prednisone and/or immunosuppressants is also recommended for class V LN with nephrotic-range proteinuria or proteinuria >1 g/24 h despite using a renin-angiotensin-aldosterone system blocker for at least 3 months (51).

Sequential therapy is used for the treatment of LN, with an induction phase followed by a maintenance phase. The induction phase is aimed at inducing rapid remission of active disease, with more intensive immunosuppressive therapy for 3 to 6 months. The maintenance phase is less intensive, with lower dosages of prednisone and more prolonged phases to prevent renal flares (51). In light of the results of recent LN trials and with

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the recent approval of belimumab and voclosporin for LN, early combination therapy (addition of newly approved drugs to conventional therapy) can be required and may be more effective in some patients.

Induction therapy. The current recommendations for induction therapy include either low-dose CYC (500 mg every 2 weeks for a total of 6 doses), MMF (2–3 g/day), or mycophenolic acid at the equivalent dose (1440–2160 mg/day) in combination with high-dose prednisone (40–60 mg/day), followed by a tapering schedule (51).

Cyclophosphamide. The Euro-Lupus Nephritis Trial compared high-dose intravenous (i.v.) CYC regimen (0.5–1 g/m^2, 6 monthly pulses and 2 quarterly pulses) with low-dose i.v. CYC regimen of 500 mg every 2 weeks for 6 doses. Both of these were combined with an initial pulse of methylprednisolone (750 mg/day for 3 days), followed by oral prednisone and maintenance treatment with azathioprine. The results revealed similar rates of renal remission and similar rates of treatment failure in both the low- and high-dose CYC groups (120). A 10-year follow-up study of patients from the Euro-Lupus Nephritis Trial revealed similar long-term outcomes in both the low- and high-dose CYC groups, as death and an increase in serum creatinine and ESRD did not differ between the 2 groups (121). Low-dose CYC is therefore preferred over high-dose CYC, but high-dose CYC can still be considered in patients with nephritic syndrome, impaired renal function with GFR between 25 and 80 mL/min, or adverse histologic factors such as crescents or necrosis in >25% of glomeruli (51, 122).

Mycophenolate mofetil. The Aspreva Lupus Management Study was one of the largest trials conducted for the treatment of LN to date, and it compared the efficacy of MMF and i.v. CYC for the use in induction therapy (27). The results of the study revealed that MMF is as effective as CYC for induction therapy in LN: 56% of patients who received MMF vs 53% of patients who received CYC responded to treatment within 6 months. Complete remission rates were similar in both groups: 8.6% of patients in the MMF group and 8.1% of patients in the CYC group achieved complete remission. The response rates were similar in Asian and White patients with MMF and CYC, but the response rate was significantly higher with MMF compared to CYC in Black and Hispanic patients (27). MMF is therefore the preferred induction agent in African-American and Hispanic patients (27) and in young men and women due to higher risk of testicular and ovarian failure following treatment with CYC (123).

Glucocorticoids. Glucocorticoids (GC) are used and needed for rapid control of inflammation during induction therapy with MMF or CYC and during maintenance therapy with other immunosuppressive drugs (51). Due to the known adverse effects associated with long-term GC use, duration of use and dose of GC should be minimized (124).

There is no clear consensus on the specific oral corticosteroid dose. Studies have revealed that a lower starting dose of GC (<0.5 mg/kg/day) is as efficacious as a higher dose (125, 126). Following pulse methylprednisolone over 3 days (total dose 250–1000 mg/day), an oral prednisone dose between 0.3 and 0.5 mg/kg/day (or 30–60 mg/day) is recommended, with the aim to reduce the dose of prednisone to ≤7.5 mg/day by 3 to 6 months (51).

Hydroxychloroquine. Hydroxychloroquine (HCQ) is recommended for all patients with SLE and LN if there are no contraindications to its use. HCQ has been found to reduce the risk of renal flares and progression to ESRD (127). To reduce the risk of ocular toxicity, a rare complication of long-term HCQ use, HCQ dose should not exceed 5 mg/kg/day of actual body weight (128). The American College of Rheumatology also recently published a joint statement with the American Academy of Dermatology, Rheumatologic Dermatology Society, and the American Academy of Ophthalmology recommending that HCQ daily

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dose should not exceed 5 mg/kg/day of actual body weight (129). They also recommended baseline retinal examination within a few months of HCQ usage to rule out underlying retinal disease. If there are no special risk factors (such as high daily dose, kidney disease, or concurrent tamoxifen usage), screening for the development of retinopathy can be deferred for 5 year but thereafter should be performed annually (129).

Emerging Therapies in Induction Therapy

Although CYC and MMF with high-dose corticosteroids are still the preferred and recommended treatment for induction therapy in active proliferative LN (51), several recent studies have shown positive results with the use of other immunosuppressive therapies such as calcineurin inhibitors (CNIs), multitarget therapies, and B-cell depletion therapy. We therefore summarize, in the subsequent sections, other emerging therapies in induction therapy in LN.

Calcineurin inhibitors. CNIs, specifically tacrolimus (TAC), cyclosporine, and, most recently, voclosporin, have been studied in LN (126, 130–133). Several clinical trials have revealed the efficacy of using TAC either as monotherapy or as part of multitarget regimen with MMF/MFA and GCs (130, 132, 134, 135).

A randomized controlled trial by Chen et al. compared the efficacy and safety of TAC vs i.v. CYC, both combined with prednisone, for induction therapy in active proliferative LN. The results were comparable between the 2 groups, as complete/overall response rates were 52.4%/90.5% in the TAC group and 38.5%/82.1% in the CYC group (132). Studies have also shown the efficacy of multitarget treatment by combining TAC with MMF and corticosteroids in active severe LN. This approach was associated with higher response rate compared to i.v. CYC induction (130, 132).

Voclosporin is a novel CNI, an analogue of cyclosporine, but with more pharmacokinetic predictability. This eliminates the need for drug monitoring compared to traditional CNIs. It has also been shown to improve glucose and the lipid profile in renal transplant patients (136, 137).

The AURA-LV study was a 48-week Phase 2 randomized controlled trial that compared the efficacy of 2 doses of voclosporin (23.7 mg twice daily or 39.5 mg twice daily) vs placebo in combination with standard of care therapy (MMF and rapidly tapered low-dose GCs for induction and remission in LN). The results showed that there were significantly higher complete renal response rates in the group that received voclosporin 23.7 mg and standard of care therapy at 24 and 48 weeks of treatment compared to the placebo group (126).

The AURORA 1 trial was a Phase 3 double-blind, placebo-controlled trial that evaluated the efficacy and safety of voclosporin in active LN. Patients were randomized to receive voclosporin 23.7 mg twice daily or placebo, in combination with MMF and rapidly tapering oral corticosteroids. Of these patients, 40.8% of the voclosporin-treated patients achieved complete renal remission at 24 weeks vs 22.5% in the placebo-treated group (133). The results of the AURORA 2 trial, a 2-year study, confirmed that patients in the voclosporin arm maintained the improvement achieved in year 1.

B-cell depletion. B-cell depletion with rituximab, a monoclonal antibody against CD20, was initial found to have positive results in observational studies in the treatment of acute LN (138, 139).

The Phase 3 Lupus Nephritis Assessment With Rituximab trial was a large multicenter placebo-controlled trial that assessed the efficacy and safety of rituximab in acute LN by comparing patients who received either rituximab or placebo with MMF and corticosteroids. The trial did not show any additional benefit in the rituximab group (140).

Obinutuzumab is a type II anti-CD20 monoclonal antibody that has been found to have promising results in the management of LN. The Phase 2

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NOBILITY trial is a randomized controlled study that evaluated the safety and efficacy of obinutuzumab in patients with proliferative LN. Patients were randomized to receive obinutuzumab or placebo infusions in combination with MMF and corticosteroids. Complete renal response was greater in the obinutuzumab group at 52 weeks, and those in the obinutuzumab group had greater improvement in GFR, urine PCR, dsDNA antibodies, and C3 and C4 compared to the placebo group at week 104, approximately 18 months after the final infusion (141).

Belimumab, a recombinant human IgG-1λ monoclonal antibody directed against the soluble B lymphocyte stimulator. Belimumab has been shown to be beneficial in nonrenal SLE in the BLISS-52 and BLISS-76 trials (142, 143). The BLISS-LN trial is a Phase 3 randomized controlled trial that evaluated the efficacy and safety of belimumab in biopsy proven active LN. Patients either received belimumab or matched placebo in addition to standard therapy (induction with high-dose corticosteroid and MMF and maintenance with low-dose corticosteroid and MMF or induction with high-dose corticosteroid and i.v. CYC using the Euro-Lupus protocol and maintenance with low-dose corticosteroid and azathioprine) (144). The primary efficacy renal response was defined as urine PCR <0.7 g/24 h, GFR rate no worse than 20% below the preflare value or >60 mg/min/1.73 m^2, and no use of rescue therapy. The results of the study showed that 43% of patients in the belimumab group achieved the primary efficacy renal response, compared to 32% of the placebo-treated patients (144).

Maintenance therapy. Following adequate response to induction therapy, the maintenance phase of treatment in LN is characterized by less intensive and more prolonged treatment with low-dose corticosteroid and immunosuppression therapy to prevent renal flares.

MMF/MFA or azathioprine are the recommended treatment for maintenance therapy (51). The MAINTAIN trial, which compared MMF and azathioprine as maintenance therapy in proliferative LN and involved 105 White European patients, showed no difference in renal flares between the groups, and similar results were found in the 10-year follow-up study (85, 145).

The Aspreva Lupus Management Study, discussed earlier, showed that in a multiethnic population, maintenance therapy with MMF was superior to treatment with azathioprine in preventing the composite end point of death, renal failure, doubling of serum creatinine level, LN flare, or the need for rescue therapy (27). In certain situations, azathioprine may be preferred over MMF, such as in females where pregnancy is being contemplated or if the cost of MMF is an issue (51).

There is no clear consensus on the optimal duration of maintenance therapy. Studies have shown that the majority of renal flares occur 5 to 6 years following treatment initiation (51, 146–148) and patients treated for at least 6 years were less likely to have renal flares when immunosuppressive therapy was discontinued. Duration of treatment should be assessed on a case-to-case basis, taking into consideration whether the patient has achieved complete renal remission, whether they have extrarenal SLE activity or presence of CKD, and the patient's personal preference (51).

Early combination therapy. Although current recommendations suggest treating patients with LN with sequential therapy, the positive findings in the AURA-LV (126) and AURORA 1–2 (133) voclosporin trials, and BLISS-LN (144) belimumab trial have highlighted the benefits of considering these treatments early in LN.

These landmark trials have also led to the approval of these therapies in LN. As highlighted earlier, with current sequential therapy, complete renal response remains low, and a significant number of patients progress to ESRD despite early treatment (14, 27, 28, 121). The promising results from these trials will likely lead to a shift in paradigm in the treatment of LN, from traditional sequential therapy to early combination therapy (149, 150).

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Other novel therapies. As for other novel therapies being studied, the sequential use of 2 B-cell targeting agents, rituximab and belimumab, for the management of LN has been investigated. The CALIBRATE trial was a Phase 2 randomized trial of 43 patients with recurrent or refractory LN who were treated with rituximab, CYC, and corticosteroids, followed by belimumab vs rituximab, CYC and corticosteroids only. This trial did not show any added benefit of sequential B cell targeted therapy in refractory LN, as there were no significant differences in efficacy between the two treatment groups (151).

Anifrolumab, a type I IFN receptor antibody, has been studied in SLE and shown positive results (152). It has also been studied in LN in the TULIP-LN Phase 2 trial (153), which evaluated the efficacy and safety of anifrolumab vs placebo along with standard therapy in proliferative LN. Although the study did not meet its primary end point, which was an improvement in 24-h urine PCR, the results of the study showed improvement across several clinical endpoints vs placebo, which included time and rate of complete renal response and rate of sustain GC taper $\leq$7.5 mg/day (153).

There are several other ongoing trials targeting other pathways in LN, which include complement target therapies, inhibition of the JAK/STAT signaling pathway, and targeted inhibition of immunoproteasome, anti-IL-17, and IL-23 (154).

CONCLUSIONS

As discussed in this review, LN remains a major cause of morbidity and mortality in patients with SLE. Urinary studies are readily available useful screening investigations for LN and therefore should be routinely used in the initial assessment and follow-up of all SLE patients. Renal biopsy remains the gold standard in diagnosing LN and should be performed early in patients who meet the criteria for biopsy. There is expanding research on the utility of serum and urinary biomarkers in the diagnosis of LN and in determining renal outcomes and response to therapy. Although several studies show promising results to support their use, these biomarkers will require validation in prospective studies with an ethnically diverse population of patients to support their use clinically.

As for the management of LN, in patients who do not respond to standard-of-care therapy, other targeted therapies such as use of CNIs, a multitarget therapies approach, or B-cell depletion therapy have showed positive results and can be considered. There are promising results on newer therapeutic targets in the management of LN, which may in the near future significantly impact how we diagnose and manage LN.

Nonstandard Abbreviations: SLE, systemic lupus erythematosus; LN, lupus nephritis; ESRD, end-stage renal disease; MMF, mycophenolate; CYC, cyclophosphamide; IFN, interferon; ISN/RPS, International Society of Nephrology/Renal Pathology Society; PCR, protein-to-creatinine ratio; 24H-P, 24-h urine sample collection for protein; GFR, glomerular filtration rate; dsDNA, double-stranded DNA; IL, interleukin; BAFF, B cell activating factor; TWEAK, tumor necrosis factor–like weak inducer of apoptosis; MMP, matrix metalloproteinases; i.v., intravenous; GC, glucocorticoids; HCQ, hydroxychloroquine; CNIs, calcineurin inhibitors; TAC, tacrolimus.

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