Lupus nephritis: clinical presentations and outcomes in the 21st century

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Abstract
Lupus nephritis (LN) is a frequent and severe manifestation of SLE. Along the decades, the epidemiology of LN and its clinical presentation have been changing. However, even though retrospective cohort studies report a decreased mortality rate and an improvement in the disease prognosis, the percentage of patients progressing into end stage renal disease (ESRD) keeps steady despite the improvements in therapeutic strategies. Current in-use medications have been available for decades now, yet over the years, regimens for optimizing their efficacy and minimizing toxicity have been developed. Therapeutic research is now moving towards the direction of precision medicine and several new drugs, targeting selectively different pathogenetic pathways, are currently under evaluation with promising results. In this review, we address the main changes and persistent unmet needs in LN management throughout the past decades, with a focus on prognosis and upcoming treatments.

Key words: lupus nephritis, renal biopsy, classification, risk factors, prognosis, B cells, calcineurin inhibitors

Introduction
The kidney is often affected in SLE and the impairment of renal function results from glomerular, tubule-interstitial and vascular lesions [1]. LN occurs in about 40% of SLE patients [2], mostly within 5 years from the diagnosis, and still presents a rate of progression to end stage renal disease (ESRD) of 4.3–10.1% [3]. Renal failure, along with infections, cancer and cardiovascular events, is one of the most common causes of death in SLE patients [4]. The incidence of LN varies with ethnicity [5] and the spectrum of clinical presentation ranges from silent urinary abnormalities to highly symptomatic cases of nephritic syndrome or rapidly progressive renal insufficiency [6].

Overview on clinical manifestations
Clinical presentation may be silent with urinalysis, renal function and 24 h-proteinuria within the normal range [7]. Otherwise, LN can be characterized by urinary abnormalities, e.g. haematuria, leukocyturia, cellular casts and mild proteinuria or more overt presentations including nephrotic syndrome or acute nephritic syndrome or rapidly progressive renal failure [8].

An Italian study evaluating a cohort of 499 LN patients from 1970 to 2016 recently reported significant changes in demographic distribution, clinical presentation and laboratory abnormalities in LN during the past 45 years.
The number of male patients and the age at LN diagnosis progressively increased along the decades with concomitant evidence of later onset of LN during the course of SLE. Over the years, clinical presentation became milder with a significant decrease in nephritic syndrome and rapidly progressive forms, a decrease in serum creatinine values and an increase in isolated urinary abnormalities, likely due to an earlier SLE diagnosis and to the identification of LN as soon as it appears during the follow-up [9], thereby highlighting the importance of a regular assessment of renal function, 24-h-proteinuria and urinary sediment in all SLE patients.

The role of kidney biopsy

The definition of renal involvement in SLE gained particular importance in the most recent sets of SLE classification criteria, where histology, together with a consistent SLE serology, is sufficient for disease classification [10, 11]. Nevertheless, the role of kidney biopsy has been questioned as most forms of LN can adequately be treated with glucocorticoids (GC) plus mycophenolate (MMF) [12]. However, because of the lack of univocal correlation between clinical presentation and histological abnormalities, renal biopsy remains fundamental in the evaluation and management of LN [13, 14]. It allows differentiation into pathological classes, the definition of the severity of renal involvement in terms of active and chronic lesions [15–17] and the identification of other rare non-LN conditions such as anti-phospholipid antibody-associated nephropathy, IgA nephropathy, thrombotic microangiopathies, drug-induced tubulo-interstitial nephritis, diabetes nephropathy or hypertensive nephroangiosclerosis [18]. A comprehensive assessment of renal biopsy may therefore guide clinicians in the choice of the more appropriate therapeutic strategy [13, 19, 20]. A threshold of proteinuria to perform a renal biopsy has not yet been defined, but when it stably reaches or overcomes the level of 500 mg/24 h or spot urine protein to creatinine ratio (UPCR) >500 mg/g (50 mg/mmol), especially with impaired renal function or active urinary sediment, it is reasonable to perform invasive investigations [17, 21]. Biopsy can also be considered in the presence of persistent haematuria or pyuria after exclusion of other potential causes or in case of unexplained renal insufficiency with normal urinalysis [15, 22].

An adequate biopsy sample should include at least 10 glomeruli and the analysis be performed by light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) when available [23].

With the exception of cases with severe activity and chronicity indexes [9], the prognostic value of the basal kidney biopsy on long-term outcome is quite modest, while a second biopsy could be more informative. Nevertheless, no standardized protocols have been defined so far [24] and re-biopsy is not part of routine care. According to international recommendations [17], a second biopsy can be considered in the presence of renal flare, unresponsiveness to treatment, worsening of renal function, persistent proteinuria or haematuria or to exclude an alternative diagnosis [25]. Recent small LN studies suggest it may be highly informative also in patients in complete clinical renal response to stratify the risk of relapse and to guide immunosuppression withdrawal [26]. Despite a clinical response to treatment, some patients still maintain mild histological signs of activity on repeated kidney biopsy [26–28] which can lead to irreversible nephron loss [29].

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis and 2018 revision

The last published classification of LN (Table 1) aimed at standardizing definitions and reducing interobserver variability. Six histological classes are defined by specific microscopic lesions and distribution of immune complexes (IC) [30]. Class I LN (Minimal mesangial) has a prevalence of 1% in adults [32] and 2.3% in children [33] and represents <20% of all cases of nephrotic syndrome that undergo renal biopsy [34]. Class II LN (Mesangial proliferative) accounts for 7–22% of all cases [35–37] and it generally presents with isolated haematuria, low-grade proteinuria and normal renal function. It is considered mild but it is associated with the risk of further progression to focal or diffuse LN [38, 39], with a cumulative incidence rate between 14.8% and 47.4% [40]. Class III and IV LN (Focal and Diffuse LN) bear the most severe prognosis and require prompt immunosuppressive treatment. A metaanalysis evaluating the prevalence of biopsy-proven LN [37] identified class IV as the most prevalent and the one associated with the highest risk of progression to ESRD. A total of 15–30% of patients with class IV do not reach remission and 15–30% of those reaching remission will develop a relapse. Class V (Membranous) is characterized by IC deposits, occurring mostly in the subepithelium, and frequent podocyte loss. Pure Class V clinically presents with nephrotic or non-nephrotic proteinuria and normal or only slightly elevated serum creatinine [41] and can be often found in association with proliferative forms. It carries a relatively low rate of progression to ESRD but it is accompanied by a high rate of complications secondary to the nephrotic syndrome such as hypoalbuminemia, thrombophilia, hyperlipidemia and infections [42]. Class VI (Advanced sclerosing) is defined by >90% of sclerotic glomeruli, often resulting in impaired renal function and variable amount of proteinuria.

Over the last 45 years, the prevalence of the histological classes has remained stable with class IV accounting for 50%, class III for 25% and class V for 20%. Nevertheless, an increase of mixed forms (III+IV and IV+V) has been reported along the years, probably reflecting the classification updating process [9]. Unchanged activity index over time was consistent with histological classes stability, while a progressive reduction of chronicity was demonstrated [9].

The last revision of the current classification, published in 2018 but not endorsed yet [31], proposes a
**Table 1** ISN/RPS 2003 Classification of Lupus Nephritis [30] and 2018 Revision [31]

| Class       | Nomenclature                  | Lesions description according to 2003 ISN/RPS                              | 2018 Revision                                                                 |
|-------------|-------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Class I     | Minimal mesangial LN          | Normal appearance of the glomeruli on LM, mesangial IC deposits on IF and fusion or effacement of podocyte on EM. | Mesangial hypercellularity; ≥4 nuclei fully surrounded by matrix in the mesangial area not including the hilar region. |
| Class II    | Mesangial proliferative LN    | Pure mesangial hypercellularity or mesangial matrix expansion with mesangial IC deposits. Absence of subepithelial or subendothelial IC deposits visible on LM. | Crescent: extracapillary hypercellularity which involves 10% or more of the Bowman's capsule circumference and composed by a mixture of cells and possible presence of fibrin and fibrous matrix. |
| Class III   | Focal LN [<50% of the glomeruli involved] | Segmental or global extracapillary or endocapillary proliferative lesions [hypercellularity][b] or inactive glomerular scars with focal subendothelial IC deposits with or without mesangial alterations. Such lesions involve <50% of the glomeruli. | Cellular crescent, >75% cells and fibrin, < 25% fibrous matrix |
|             | A: Active lesions[a]          | Segmental lesion: lesion that affect less than half of the glomerular tuft. | Fibrous crescent, >75% fibrous matrix, < 25% cells and fibrin |
|             | A/C: Active and Chronic lesions[a] | Global lesion: lesions that affect more than half of the glomerular tuft. | Fibrocellular crescent: 25–75% cells and fibrin and the remainder fibrous matrix |
|             | C: Chronic lesions[a]         |                                                               | Adhesion: an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis. |
| Class IV    | Diffuse LN [≥50% of the glomeruli involved] | Segmental or global extracapillary or endocapillary proliferative lesions [hypercellularity][b] or inactive glomerular scars typically with diffuse subendothelial deposits with or without mesangial alterations. Such lesions involve ≥50% of the glomeruli. | Fibrinoid necrosis: fibrin associated with glomerular base membrane disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis. |
|             | Diffuse segmental LN          | Segmental lesion: lesion that affect less than half of the glomerular tuft. |                                                               |
|             | Diffuse global LN             | Global lesion: lesions that affect more than half of the glomerular tuft. |                                                               |
|             | A: Active lesions[a]          |                                                               |                                                               |
|             | A/C: Active and Chronic lesions[a] |                                                               |                                                               |
|             | C: Chronic lesions[a]         |                                                               |                                                               |
| Class V     | Membranous LN                 | Continuous or granular subepithelial IC deposits with or without mesangial alterations and IC deposits | Tubulointerstitial lesions: indicate whether interstitial inflammation occurs in presence or absence of interstitial fibrosis. |
| Class VI    | Advanced sclerosing LN [≥90% glomeruli involved] | Globally sclerosed glomeruli without residual activity | Podocytopathy: glomerular changes consistent with minimal change disease, mesangial proliferation or focal segmental glomerulosclerosis on LM and podocyte effacement on EM, with or without mesangial IC deposits. No evidence of IC deposition in peripheral glomerular capillaries or endocapillary proliferation. |

[a]see Table 2.  
[b]The term ‘proliferative’ has been substituted by hypercellularity in the 2018 revision.  
[c]Differentiation among diffuse segmental and diffuse global has been eliminated in the 2018 revision.  
EM: electron microscopy; IC: immune complex; IF: immune fluorescence; LN: lupus nephritis; LM: light microscopy.
The improvement in survival over the past decades among LN patients was mainly due to the introduction of effective and less toxic drugs and more tolerated regimens. GC monotherapy, especially in the form of intravenous (i.v.) pulses, was implemented after 1980 with the association of immunosuppressants such as azathioprine (AZA) or CYC [9, 50, 51]. The concept of maintenance therapy has established beside induction, becoming part of the clinical practice. In the past decade, the use of AZA for induction and maintenance has decreased in favour of MMF [9], which has become a mainstay in the treatment as it was shown to be as efficacious but less toxic than CYC in the induction phase [52, 53] and more effective than AZA during maintenance for flare prevention [9, 54]. At the turn of the new millennium, in view of optimizing efficacy and reducing side effects, the low-dose i.v. CYC induction protocol was approved for the treatment of LN as it was demonstrated to be safer and equally effective compared with the high-dose regimen hitherto in use [55].

According to current recommendations, the therapeutic strategy for LN aims to achieve rapid remission or at least partial response within 6–12 months (discussed below), to prevent flares and preserve renal function, reduce morbidity and mortality and preserve fertility [17, 56]. The choice of the treatment mainly depends on the histological class, on activity and chronicity indexes and includes immunosuppressants, adjuvants and symptomatic drugs.
For Class II, current recommendations do not suggest immunosuppression [15, 17], while previous recommendations indicated low-to-moderate dose of GC alone or in combination with AZA if proteinuria >1 g/24 h, especially in the presence of glomerular haematuria [22].

For class III and IV, there is unanimous agreement on an induction treatment based on high dose pulses of methyl-prednisolone followed by oral GC and MMF or i.v. CYC [17].

During the past 10–15 years, the efficacy and safety of Tacrolimus (Tac) + GC and Tac + MMF + GC vs CYC + GC and MMF + GC was evaluated, mostly in Chinese patients, as induction and maintenance therapy, demonstrating a good response in terms of remission and normalization of serological abnormalities [57–60]. Calcineurin inhibitors (CNI), already mentioned in the 2012 EULAR and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for LN [22], have a more prominent spot in the 2019 update as they demonstrated a favourable efficacy/toxicity profile especially in patients with nephrotic range proteinuria [61] and could be a valid option in combination with MMF for induction as multitarget therapy [17]. In non-responding or refractory patients, it is advised to switch to another first-line treatment including MMF, CYC or CNI as monotherapy or multitarget therapy. An alternative option for refractory disease [62, 63], even though not approved for LN due to its failure in randomized control trials (RCTs) [64, 65] is rituximab (RTX), a chimeric anti-CD20 monoclonal antibody. Its use is suggested by EULAR and ACR recommendations [15, 17] and it is prescribed off-label in clinical practice as a rescue treatment in a remarkable proportion of SLE and LN patients [65–69]. A recent meta-analysis assessing the clinical efficacy and safety of RTX in the treatment of LN [62] reported a significant decrease in renal disease activity and proteinuria as well as efficacy in preventing organ damage. Moreover, RTX may help GC tapering [70], potentially reducing treatment complications.

Maintenance treatment is based on oral GC plus MMF or AZA for at least 3–5 years after complete remission. Notably, the 2019 updated LN recommendations state that, after this timespan, a gradual tapering of GC and then of immunosuppressants should be attempted, keeping a tight follow-up during de-escalation [17, 71, 72].

For Class V LN, immunosuppressive treatment is indicated in patients with nephrotic syndrome and in those with proteinuria >1 g/day despite renin-angiotensin-aldosterone system therapy in order to reduce proteinuria and avoid nephron loss, with a particular endorsement for CNI which stabilize podocyte structure and function [73, 74]; MMF or i.v. CYC could be equally valid alternatives [17]. Additionally, symptomatic therapy with inhibitors of renin-angiotensin-aldosterone system is also recommended [17, 75]. Importantly, when Class V is combined with class III or IV it should be treated as class III and IV.

Histologic class VI usually requires preparation for renal replacement therapy [15, 17, 22].

In LN, HCQ in addition to the conventional immunosuppressants was shown to retard damage accrual, increase the probability of renal remission [76] and prevent renal flares in particular at a target plasma level of 0.6 mg/l [77]. If given prior to LN development, HCQ is associated with a lower risk of renal failure and death [78]. The use of HCQ is emphasized in 2012 ACR guidelines for LN and 2019 update of the EULAR recommendations for the management of SLE and LN [17, 56] where at a dose ≤5 mg/kg, adjusted in patients with glomerular filtration rate (GFR) <30 ml/min, it is strongly suggested as a background therapy in all patients in absence of contraindications, performing a regular ophthalmologic assessment. HCQ is also allowed and recommended during pregnancy as it reduces flares, thrombosis and the risk of congenital heart block in anti-Ro positive mothers [79]. Pregnancy is a condition that should be properly planned, especially in patients with active LN [17, 22] as renal disease activity at the time of conception is associated with a poor mother and foetus outcome [80]. Gestational planning aims at scheduled withdrawal of those immunosuppressants incompatible with pregnancy and at safe programming of conception during LN remission (GFR and UPCR in the preceding 6 months should be <50 ml/min and <500 mg/g (<50 mg/mmol), respectively). Immunosuppressants allowed during pregnancy and lactation are prednisone, AZA and CNI; acetylsalicylic acid is recommended in active LN to reduce the risk of pre-eclampsia in absence of contraindications [17, 22].

Renal flares, partial remission and complete remission

A complete renal response is defined, according to the 2019 update of EULAR/ERA-EDTA recommendations for LN, by a UPCR <500–700 mg/g (<50–70 mg/mmol) by 12 months with normal or near-normal GFR, while partial renal response is defined by a reduction in proteinuria of at least 25% by 3 months or 50% by 6 months; notably, the reported timeframes should be extended to 6 and 12 moths, respectively, for patients who present with nephrotic-range proteinuria [17]. Although current induction therapy is overall effective for the achievement of a complete or partial remission after 6–12 months, renal flares are quite common with a cumulative reported rate ranging from 27% to 66% [81] and are associated with impaired renal survival [82]. Renal flares are categorized, according to a European consensus statement, into proteinuric and nephritic, the latter in turn subdivided into non-severe and severe [83].

The main factors associated with the risk of renal relapse are young age at onset (<30 years), male sex, African-American ethnicity, delayed treatment initiation, long time to remission, low C4, partial response, high SLE disease activity score, rise in anti-dsDNA titer, arterial hypertension, severe extrarenal SLE (central nervous system involvement) and low-dose immunosuppression [82].

Some studies evaluated the difference of prognosis between patients who underwent partial remission and
those who did not achieve any remission status, finding that partial renal remission at 24 months after biopsy, according to the modified Aspreva Lupus Management Study (mALMS) and Belimumab Lupus Nephritis Study (BLISS-LN), is significantly less likely to result in ESRD or mortality in comparison to remission [84]. In a small study involving 86 patients with diffuse LN, the renal survival at 10 years was 94% in patients with complete remission, 43% in case of partial remission and 19% in those with no remission [85]. Similarly, CKD-free survival in a large multicentric cohort did not differ significantly between partial or complete responders while being significantly improved vs non-responders, thereby confirming that any degree of renal response is always advisable [86].

Importantly, time to response is likely to influence renal prognosis. Although some studies reported that proteinuria of 0.7–0.8g/day at 12 months was the individual best predictor of long-term renal outcome in LN [87, 88], it was demonstrated that the optimal cut-off varied based on baseline proteinuria values [89]. In the Hopkins Lupus Cohort, two composite remission scores including serum creatinine and proteinuria performed better in predicting renal survival than proteinuria alone [84]. Similarly, in 550 LN patients, 12-month proteinuria and 12-month serum creatinine were able to predict the risk of developing CKD at three years [90].

Prognosis, survival and outcome trends in patients with LN: past and present

LN plays a major role in defining prognosis and survival of SLE patients. Data form the last 50 years highlight a substantial decrease in mortality rate with a concomitant increase in CKD- and ESRD-free survival at 10 and 20 years. Accordingly, the number of patients achieving a complete renal remission increased from 48.5% in 1970s to 58.5% in the mid-2010s [9]. Prior to the introduction of GC, the 5-year survival rate of patients with LN was 44% but after their routine use in combination with immunosuppressants, it improved to 80% in the 1980s and to >90% now [9, 91, 92]. These results are mainly attributable to the concept of early diagnosis and the use of more effective and early treatments along with the increased knowledge in the management of complications (i.e. infections) and comorbidities [9, 93].

Nevertheless, in the last 10 years trends stabilized both in terms of ESRD and survival rates [91, 94, 95]. In a retrospective study of a cohort of 325 SLE patients followed in Oslo from 1999 to 2008 [96], the incidence rate of ESRD was 2.3 per 1000 patient-years. The cohort presented an overall standardized mortality ratio (SMR) of 2.1 but the SMR significantly differed between patients who did and did not develop LN (SMR 3.8 and 1.7, respectively). The highest estimates were noted in patients aged between 16 and 39 years (SMR 13.4) and with ESRD (SMR 5.4). These data confirm that LN is a major determinant in SLE prognosis and that once ESRD has established, the disease markedly worsens.

Risk factors for progressive renal disease

Demographic risk factors

Renal outcome of patients with LN varies among different ethnic groups, with the best prognosis for Caucasians and the worst for Africans, whereas Asians have an intermediate prognosis [5, 97–99]. Black patients present, along with Hispanic patients, worse outcomes with increased rates of ESRD and mortality [100]. This is probably the result of higher incidence of proliferative diffuse LN, burdened by nephritic syndrome with severe hypertension mediated by a genetic predisposition [101], as well as to limited access to adequate care and lower adherence to treatment [93, 97, 102]. Male gender is another established demographic risk factor for worse renal outcome [103, 104].

Clinical risk factors

To date, the main clinical risk factors for the development of CKD are baseline hypertension and poor control of cardiovascular risk factors during the follow-up; nephrotic range proteinuria, young age, anaemia and elevated serum creatinine at the time of biopsy [9, 99, 105]; an inadequate immunosuppressive treatment at diagnosis that could lead to a lack of a complete renal remission and to repeated nephritic flares [9, 82, 106].

A multicentric study on 381 LN patients has recently shown that lack of EULAR/ERA-EDTA complete or partial renal response at 12 months [22] and uncontrolled hypertension independently predicted CKD development [86].

The aforementioned risk factors, along with the histological class, are also the main contributors to the development of ESRD [9, 35].

Histopathological risk factors

A well-recognized association links histopathological findings on kidney biopsy to the clinical course of LN, with mesangial nephritis (class II) carrying the best renal prognosis while proliferative nephritis (class III and IV) presenting with a more aggressive course and deterioration of renal function [9]. Membranous (class V) nephritis has long been considered mild; however, it may lead to severe protein loss, nephrotic syndrome, prolonged hospitalization and eventually chronic renal damage [107].

High activity and chronicity indexes are independent predictors of CKD and ESRD [9]. Considering histopathological changes individually, cellular crescents (active injury) and interstitial fibrosis (chronic damage) in the initial renal biopsy bear the highest predictive value [108, 109]. Extracapillary proliferation at repeated renal biopsy is an even stronger predictor of renal function deterioration, therefore requiring an aggressive treatment [24]. Alterations of the tubulointerstitium including inflammatory infiltrate and tubular atrophy appear to also be predictors of poor prognosis, independent on class [110, 111].

The histological analysis of kidney biopsy of LN patients over the last five decades showed significant
decrease in chronicity indexes, probably due to a tighter surveillance of renal function in SLE patients, likely contributing to the improvement of overall renal survival [9].

It should be mentioned, however, that some limitations in the definition of the risk factors still remain, in particular owing to the intra- and inter-observer variability in the evaluation of the biopsy specimens, the absence of a validated cut-off point for active and chronic lesions to predict renal failure or mortality and the fluctuating course of renal involvement with a possible reversibility of some histological features [112].

What’s in the pipeline?

To better stratify patients and overcome the limits of current therapies, the research is now focusing on the comprehension of pathogenetic mechanisms underlying LN. Therefore, single-cell analysis, biomarker research, characterization of the role and function of autoantibodies and genetic and epigenetic profiling are providing essential information [1, 113–115]. Thanks to these achievements, further advances, increasingly oriented towards precision medicine, are going to enrich the available therapeutic armamentarium [116, 117] (Table 3) (Fig. 1).

The AURA-LV study [118, 128] evaluated the efficacy of high-dose and low-dose voclosporin + MMF vs MMF alone in inducing complete remission at 24 weeks, reaching its primary end point and showing a relevant steroid sparing effect. Importantly, steroid tapering in the AURA trial was dramatically fast, reaching 2.5 mg/day at 16 weeks. This not only did not affect the renal outcome of participants, but rendered apparent the incremental benefit of voclosporin [72]. Two other phase III trials are further evaluating effectiveness and long-term safety and tolerability of voclosporin [119, 120].

Among monoclonal antibodies, belimumab, a fully human IgG1-lambda antibody against B-lymphocyte stimulator (BlyS), is the only biologic drug so far approved for SLE patients with active disease despite SoC. The positive results of a phase III RCT in LN involving 448 patients [121] have recently been announced. Comparing patients receiving belimumab plus SoC to those taking placebo plus SoC, a significantly higher proportion of patients in the belimumab arm achieved the primary end point, i.e. renal response at 104 weeks, and some relevant secondary end points.

**TABLE 3** Ongoing and recently completed clinical trials of new therapies for LN

| Name of the trial                      | Drug tested             | Therapeutic target | Phase of the trial | Number of enrolled patients | Primary outcome                                                                 | Ref   |
|----------------------------------------|-------------------------|--------------------|--------------------|------------------------------|---------------------------------------------------------------------------------|-------|
| AURA-LV (completed)                    | Voclosporin             | T-cell             | II                 | 265                          | Number of subjects achieving complete remission at 24 weeks                      | [118] |
| AURORA (completed)                     |                         |                    | III                | 358                          | Number of subjects achieving renal response within a time frame of 52 weeks     | [119] |
| AURORA 2 extension study (completed)   |                         |                    | III                | 227                          | Adverse event profile and routine biochemical and haematological assessment within a time frame of 36 months | [120] |
| BLISS-LN                               | Belimumab               | BAFF               | III                | 448                          | Number of participants with primary efficacy renal response at week 104        | [121] |
| CALIBRATE (completed)                  | Ritu pamphab +         | CD20, BAFF         | II                 | 43                           | Proportion of patients with a SLEDAI-2K score of <2 without the use of additional immunosuppression | [122] |
| NCT04221477                            | Obinutuzumab            | CD20               | III                | 250                          | Percentage of patients with complete renal response at week 76                  | [123] |
| NCT02550652                            | Anifrolumab             | IFN-I receptor     | II                 | 126                          | Percentage of patients with complete renal response at week 52                  | [124] |
| TULIP-LN1                              | TYK2-inhibitor          | TYK2               | II                 | 78                           | Incidence of adverse events, incidence of laboratory abnormalities, partial renal response | [126] |
| NCT03943147                            | TYK2-inhibitor          | TYK2               | II                 | 78                           | Incidence of adverse events, incidence of laboratory abnormalities, partial renal response | [126] |
| CALIBRATE (completed)                  | Ritu pamphab +         | CD20, BAFF         | II                 | 43                           | Proportion of patients with a SLEDAI-2K score of <2 without the use of additional immunosuppression | [122] |
| NCT04221477                            | Obinutuzumab            | CD20               | III                | 250                          | Percentage of patients with complete renal response at week 76                  | [123] |
| NCT02550652                            | Anifrolumab             | IFN-I receptor     | II                 | 126                          | Percentage of patients with complete renal response at week 52                  | [124] |
| TULIP-LN1                              | TYK2-inhibitor          | TYK2               | II                 | 78                           | Incidence of adverse events, incidence of laboratory abnormalities, partial renal response | [126] |
| NCT03943147                            | TYK2-inhibitor          | TYK2               | II                 | 78                           | Incidence of adverse events, incidence of laboratory abnormalities, partial renal response | [126] |
| SELUNE                                 | Secukinumab             | IL-17              | III                | 460                          | Proportion of subjects achieving complete renal response                        | [127] |

BAFF: B-cell activating factor; CD: cluster of differentiation; IL: interleukin; Ref, reference; TYK2: tyrosine kinase 2.
These positive results were expected on the basis of the outcomes of real-life observational studies where belimumab was effective in the decrease of proteinuria levels and number of renal flares [129, 130].

Another potential option under evaluation is the sequential treatment with RTX followed by belimumab [122, 131]. It is based on the assumption that BLyS levels increase following RTX administration as a feedback mechanism; hence, a sequential therapy should drive to a depletion of CD20 expressing B cell and then avoid the rebounded B cell enhanced repopulation [132, 133]. The co-administration of the two drugs may also have a synergistic effect [134].

Among biologic drugs tested for LN, obinutuzumab [123, 124] is a type II anti-CD20 monoclonal antibody that differs from RTX because it enhances CD20-expressing B-cell depletion via antibody-dependent cell-mediated cytotoxicity and programmed cell death, instead of complement-mediated cytotoxicity. Positive results of a phase II trial for the treatment of proliferative LN aiming at complete or partial renal response at week 52 have been presented at the 2019 ACR meeting in Atlanta [135,136].

Given the role of type I IFN in the pathogenesis of SLE, anifrolumab, a fully human monoclonal antibody that blocks type I IFN response through binding to type I IFN receptor, is currently under evaluation. Phase III RCT TULIP-1 was proven effective in decreasing disease activity in non-renal SLE, especially in patients with an enhanced IFN gene signature [136], and a phase II RCT is ongoing in LN [125].

Additionally, JAK inhibition is underway in SLE, culminating in down-regulation of inflammatory cytokines-driven pathways and IFN-dependent genes. Despite an overall good safety profile, JAK inhibitors have been burdened by signals of reactivation of opportunistic infections, probably due to their broad inhibitory potential [137]. In this regard, a study started in July 2019 [126] is testing safety and effectiveness of a selective Tyk-2 inhibitor in LN. Notably, the molecule stabilizes a regulatory pseudokinase domain of Tyk-2 without affecting its catalytic activity and thereby more selectively blocking the IL-12/23 and type I IFN pathways, likely raising fewer safety issues.

Concerning the selective inhibitors of interleukins, recent studies began to shed light on the role of IL-17 in the pathogenesis of SLE and LN [138–140] and a phase III RCT has just started to evaluate efficacy and safety of subcutaneous 300 mg secukinumab compared with placebo in combination of SoC therapy in active proliferative LN [127].

**Conclusions**

Despite important advances, LN is still a serious risk factor for the development of ESRD and for early mortality and disability in SLE. A proper management of LN...
by an expert dedicated team should lead to a preserved renal function in the long term, but requires an early recognition and evaluation through renal biopsy, followed by the optimized use of available treatments. Minimization/withdrawal of GC treatment is endorsed by the updated recommendations and should be attempted after an adequate time spent in renal remission. Besides traditional immunosuppression, biological drugs targeting selected pathways as well as multitargeted therapies are under evaluation and some already provided evidence of efficacy in RCTs and clinical practice, submitting a likely widespread use in the near future. This should be coupled with a personalized approach, taking into account global patients as well as renal features, in order to overcome the current limits to a truly improved prognosis.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript. This paper was published as part of a supplement supported by an educational grant from GSK.

Disclosure statement: The authors have declared no conflicts of interest.

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