Chapter

Lupus Nephritis: Current Updates

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Abstract

Lupus is a heterogenous multisystem autoimmune disease whereby nephritis is one of its most common cause of overall morbidity and mortality. Accurate, timely diagnosis and effective treatment in lupus nephritis (LN) remains a challenge to many clinicians including those who are directly involved in the daily care of these patients. Despite significant improvement in patients' survival rate in recent years, in this era of precision medicine, there is pressing need to further improve our understanding and management of this disease. Our chapter would shed light on the key issues in LN including recent advances in our scientific understanding of its' pathophysiology, major challenges and treatment strategies.

Keywords: SLE, lupus, nephritis

1. Introduction

Lupus nephritis (LN) is the most common severe organ manifestation of systemic lupus erythematosus (SLE). It may be the presenting manifestation of SLE and usually arises within 5 years of diagnosis [1]. Approximately 40–70% of SLE patients will develop LN [2] with histopathological changes observed in most patients even among those without renal manifestations (known as "silent LN"; mostly with "milder" class I and II histologic lesions) [3, 4]. Clinical presentation of LN is highly variable, ranging from asymptomatic proteinuria with normal renal function to rapidly progressive renal failure.

Recent data demonstrates reduction in the temporal mortality trend among end stage renal disease (ESRD) LN patients [5]; however, the risk of progression to ESRD in LN remains unchanged [5, 6]. Despite significant improvement of outcome in this modern era, less than 50% of patients achieve complete clinical remission following immune suppression [7] with 10–20% of patients progressing to ESRD [8]. This chapter explores recent studies that have substantially contributed to our understanding of LN and provides new insights into the epidemiology, pathogenesis, classification criteria and management strategies of LN.

2. Epidemiology

The prevalence of SLE and LN varies based on age, gender, geographical location, socioeconomic status and ethnicity. There are also disproportionate differences in the incidence and prevalence, depending upon the validated classification criteria or methods of case ascertainment used.

2.1 Systemic lupus erythematosus (SLE)

In a large retrospective study performed in the United Kingdom (UK) involving more than 7,000 SLE cases between 1999 and 2012, the overall annual incidence of SLE was 4.9 cases per 100,000 population per year with overall prevalence of 97 per 100,000 population; highest in Afro-Caribbean ethnic subgroup (517 per 100,000), followed by the Indian subgroup (193 per 100,000) while Caucasian subgroup was 134 per 100,000 [9]. Other studies found similar estimates with annual incidence between 4 and 8 cases per 100,000 population per year. Expectedly, the worldwide prevalence of SLE also varies between 30 to 90 cases per 100,000 population, highest in the African populations, lowest in Caucasians, with Hispanic and Asian subgroups in between the two extremes [10, 11].

All studies worldwide have demonstrated marked predominance of women in SLE, between 6 and 9 times higher than men. In the United States (US) and UK, the peak incidence was in women aged between 40 and 59 [10, 12]; in contrast, a population based study in Taiwan involving almost 7000 SLE patients revealed earlier peak incidence in women aged between 20 and 29 [13], a consistent trend among other studies in the Asia-Pacific region [14].

2.2 Lupus nephritis (LN)

Renal involvement occurs in 25–50% of SLE patients at the time of diagnosis [15]. The cumulative incidence, again, varies according to ethnicities. In a US study involving three ethnic subgroups, the incidence of LN was found to be the highest among the African subgroup (69%) followed by Hispanics (61%) and Caucasians (29%) [16]. In the Asia-Pacific region, the cumulative incidence of LN varies between 30% and 82%, lowest in Australian and highest in Malaysian populations respectively [14].

Despite higher overall incidence of SLE in women than in men, strikingly, renal involvement was found to be 50% higher in SLE men in a meta-analysis involving nearly 12,000 SLE patients across multiple countries [17]. Left untreated, LN carries significant morbidity and mortality, with the mortality rate estimated to be 6 times higher than general population. However, with the current therapeutic options, the 10-year survival for patients with LN can exceed 98% [18].

3. Pathogenesis

The pathogenesis of LN is complex and achieving full understanding of its pathophysiologic mechanisms has proved challenging due to the molecular and phenotypic heterogeneity. Genetic predisposition, epigenetic dysregulation and environmental triggers are all likely to contribute to the disease expression [1, 19, 20]. Dysregulation of both innate and adaptive immune responses manifested by disturbance in apoptotic cell clearance, cytokines stimulation, B-cell immunity and T-cell function leads to glomerular and/or tubulointerstitial injury.

Production of autoantibodies targeting self-DNA, other self-nuclear antigens and non-nuclear materials results from loss of immune self-tolerance and autoimmunity in genetically predisposed individuals. Formation of immune complexes (ICs) may occur in circulation and deposits in various organ systems including the kidneys. Antibodies can also directly target in situ nephritogenic antigens at the major resident renal cells (mesangial cells, glomerular endothelial cells, tubular epithelial cells and podocytes) [21]. Co-stimulation by Fc receptors (FcRs) and endosomal Toll-like receptors (TLRs) leads to activation of the complement

system and subsequent release of cytokines and chemokines leading to renal tissue injury [22–25]. Anti-C1q antibodies, while not exclusive to LN, are strongly associated with renal inflammation and severe LN, amplifying complement activation in situ [26, 27].

Overactivation of 1) Interferon (IFN)-I signalling pathway, which is regulated by dendritic cells (DCs), interleukins (eg. IL 12/23), JAK1, TYK2 and various STAT proteins and 2) NFκB are both implicated early in the innate immune response and play major roles in the pathogenesis [28, 29]. Adaptive responses including persistent activation and interaction of aberrant polyclonal B and T cells involving multiple co-stimulatory molecules promote chronic inflammation and renal tissue damage. Studies have also uncovered that formation of long-lived memory T-cells and plasma cells that reside in survival niches in bone marrow and inflamed tissue render them resistant to conventional immunosuppression or B cell therapies [30].

B cell activation factor (BAFF)/B-lymphocyte stimulator (BLyS) promotes formation of tertiary lymphoid structures (TLSs) that contribute to lymphocyte priming and autoantibody production within the kidneys [31] while evidence in patients and animal models have demonstrated high levels of IL-17 producing T cells in LN [32]. Several other regulators of apoptosis have also been implicated in the development of LN including dysregulation of autophagy, BCL-2, phosphatase and tensin homologue (PTEN), mannose-binding lectin (MBL) and neutrophil extracellular traps (NETs) among several others [33–40].

More than 10 genome-wide association studies (GWAS) have been conducted thus far with more than 50 genes implicated involving various pathogenic mechanisms in the pathogenesis of SLE, some associated with LN [2, 41]. These candidate genes are likely to undergo further evaluation and validation from deep sequencing and mechanistic studies. *Mohan et al.* have elegantly categorised the implicated genes into four functional groups; genes that influence 1) lymphocyte activation, particularly B cells (eg. BLK, STAT4, TNFSF4, HLA-DR) 2) innate immune signalling (notably NFκB and IFN-I; eg. IKZF1, IRF5, TLR9, TNFAIP3) 3) intra-renal signalling (eg. ACE, KLK) and 4) handling of apoptotic material, chromatin and ICs (eg. ATG5, ITGAM, FCGR2A/3A/3B); genetic interaction from multiple categories is required for severe LN to develop [2].

The TLR7 gene, which is located at chromosome X, has recently been the focus of considerable research in SLE and LN. Theories regarding the contribution of TLR7 gene have included 1) Enhanced TLR7 protein expression in renal DCs and macrophages which correlated with renal disease parameters in murine models [42] 2) Emerging evidence that TLR7 dosage is a key pathogenic factor to the pathogenesis of SLE: *Dillon et al.* assembled the largest group consisting of 316 men with SLE and found high prevalence of SLE in X chromosome aneuploides such as Klinefelter's syndrome (KS; 47, XXY) and de la Chapelle's syndrome (46, XX male) [43] while recently, Souyris and colleagues provided proof that TLR7gene evades X chromosome inactivation in immune cells in women and KS men, and proposed this as a mechanism for the elevated risk of SLE in women and KS [44], which may partially explain the high preponderance of SLE in females.

4. Diagnosis and classification

Current non-invasive SLE biomarkers such as proteinuria or active urine sediment, serum creatinine, anti dsDNA and hypocomplementemia could not reliably confirm the presence, severity and/or chronicity, or predict the outcome of LN. Many novel biomarkers are currently being explored in the management and

as therapeutic target in LN; unfortunately, none so far had been utilised in daily clinical practice [45].

In patients suspected of LN, certain clinical and laboratory features may however predict the class of LN a patient may have. In a retrospective study analysing 297 renal biopsies of SLE patients with some degree of proteinuria, absence of malar rash, negative anti-dsDNA and urine leukocytes of <5/high power field under microscopy are independent predictors for class II LN. Class III or IV can independently be predicted by younger age at diagnosis (<32 years), musculoskeletal involvement, hypertension, presence of anti-dsDNA, elevated creatinine level, absence of nephrotic range proteinuria and presence of leucocytes and cellular cast in urine. Older age, malar rash and low C3 level may be predictive for class V LN [46].

4.1 Role of renal biopsy

Renal biopsy is the gold standard for the diagnosis and current classification of LN. The histological findings may assist physicians to optimise therapeutic strategies in individual patients, including assessing disease activity and/or chronicity for guidance to escalate or de-escalate immunosuppression accordingly. It is an invasive procedure with potential risks, most notably bleeding; however, given the lack of available biomarkers to identify disease activity, it remains an irreplaceable tool and mainstay of current management in LN.

Indication for a renal biopsy includes significant proteinuria of >0.5 g/day (or equivalent), certain unclear acute elevation of serum creatinine level, and in patients with severe disease relapse (**Table 1**) [47]. Biopsy is rarely done in patients with isolated haematuria or proteinuria of <0.5 g/day; hence, class I LN is rarely seen in the histology. Performed by either experienced nephrologist or interventional radiologist, adequate tissue is obtained in >95% of times.

Given the location of kidney where no direct compression can be performed post biopsy, bleeding (as detected by routine CT scan or ultrasound post biopsy) was found to be common, ranging in 57–91% of patients [48]; however, the actual incidence of clinically important bleeding is small. Meta-analysis of 34 relevant studies found low rates of macroscopic haematuria (3.5%) and blood transfusion (0.9%), with lower rates yielded in need for interventions (0.6%) such as catheter insertion for bladder obstruction (0.3%) and nephrectomy (0.01%) and death (0.02%) [49].

The bleeding risk increases in females, use of larger needle (14-G), elevated serum creatinine (>176 umol/L) or acute renal failure, uncontrolled systolic blood pressure (>170 mmHg) [49, 50] and in patients with coagulopathies or are on anticoagulation/antiplatelet agents. Most serious complications are detected within 4 hours of biopsy, and majority within 12 hours [51, 52]. Routine 1-hour post biopsy ultrasound for presence of haematoma to predict complication has not been shown to be clinically beneficial (positive predictive value of 43%; negative predictive value of 95%) [53].

Should biopsy	May biopsy
Proteinuria >0.5 g/24 hours	Isolated haematuria or pyuria
Unexplained renal insufficiency	Proteinuria less than 0.5 g/24 hours
Differentiating activity vs. chronicity	'Protocol' biopsy during/after treatment
Severe relapse	Mild relapse

Table 1.
Possible indications for kidney biopsy in SLE patient.

The role of repeat renal biopsy in LN flares is controversial. In essence, a repeat biopsy is required if it may change management; for example, this is particularly true in a patient with stable renal function who developed sudden deterioration of creatinine associated with active urine sediment. This may reflect the possibility of crescentic glomerulonephritis (GN) that warrants stronger immunosuppression. During LN flare, histological transformation is more likely to occur if the initial histology revealed non-proliferative disease (initial class II); although, many would still have persistent active lesions in proliferative disease [54, 55].

Renal biopsy may also be considered to determine disease chronicity in patients with persistent proteinuria and lower glomerular filtration rate (GFR), which warrant de-escalation of immunosuppression. It is well documented that repeat biopsies lead to change to immunosuppression in more than half of the cases [55].

Decision to stop maintenance immunosuppression in LN is often challenging and some researchers perform 'protocol biopsies' after a period of complete clinical remission to guide withdrawal of treatment. Its' value however is still debatable, as studies mostly looked at the prognosis based on the histological features [54]. In a study by *De Rosa et al.*, 36 LN patients on immunosuppressive therapy for more than 3 years and in clinical remission (proteinuria <0.5 g/day) were re-biopsied. Regardless of the results of biopsy, the immunosuppressive medications were tapered down. Those patients with residual activity in histology had higher chance of relapses upon reducing therapy [56], which supports histology-based approach in treatment withdrawal.

4.2 Classification criteria

4.2.1 SLE and renal involvement

The revised American College of Rheumatology (ACR) 1997 criteria specifies that a patient can be diagnosed with SLE if 4 of 11 criteria are met at any interval of observation (**Table 2**). Renal involvement can be considered if patient developed proteinuria of >0.5/day or appearance of cellular cast (red cells, haemoglobin, granular, tubular or mixed) [57]. The 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria divided SLE features into 11 clinical and 6 immunologic criteria, where SLE can be fulfilled by a) biopsy-proven LN in presence of ANA or anti-DNA antibodies or b) meeting ≥4 of 17 criteria, with at least 1 criterion from each division [58].

European League Against Rheumatism (EULAR)/ACR published a new set of criteria for SLE diagnosis in 2019 [58]. It employs the strategy that ANA must be positive for the diagnosis to be considered, followed by 10 domains with different individual weightage; diagnosis can be made if total score reaches 10 points, again with renal involvement carrying a high weight between 4 and 10 depending on the renal manifestations (**Table 2**) [59].

4.3 Diagnosis of lupus nephritis

The clinical presentations of LN may differ ranging from asymptomatic haematuria to rapidly progressive GN. All patients with SLE should have urinalysis checked on regular basis to detect renal involvement. Presence of significant proteinuria would trigger the need for a renal biopsy, although many would perform biopsies for reasons such as persistent haematuria and elevated serum creatinine [54]. Biopsy is critical to distinguish between active nephritis, non-glomerular pathology of SLE (such as tubulointerstitial nephritis or thrombotic microangiopathy) and disease chronicity (such as interstitial fibrosis, tubular atrophy and

ACR 1997	SLICC 2012	ACR 2019
4 out of 11 criteria	4 out of 17 criteria, with at least 1 from each domain	Fulfil the entry criterion, followed by 10 points in additive criteria
Malar rash	**Clinical Domain**	**Entry criterion**
Discoid rash	Acute cutaneous lupus	ANA positive
Photosensitivity	Chronic cutaneous lupus	**Additive criteria**
Oral ulcer	Oral ulcer	**Clinical domain**
Arthritis	Synovitis	Constitutional
Serositis	Non-scarring alopecia	*Fever* (2)
Renal disease	Serositis	Haematologic
Neurologic disorder	Renal	*Leukopenia* (3)
Haematologic disorder	Neurologic	*Thrombocytopenia* (4)
Immunologic disorder	Haemolytic anaemia	*Autoimmune haemolysis* (4)
ANA positive	Leukopenia or lymphopenia	Neuropsychiatric
	Thrombocytopenia	*Delirium* (2)
	Immunologic Domain	*Psychosis* (3)
	ANA	*Seizure* (5)
	Anti dsDNA	Mucocutaneous
	Anti-Sm	*Non-scarring alopecia* (2)
	Antiphospholipid antibody	*Oral ulcers* (2)
	Low complement	*Subcutanoues OR discoid lupus* (4)
	Direct Coomb's test	*Acute cutaneous lupus* (6)
		Serosal
		Pleural/Pericardial effusion (5)
		Acute pericarditis (6)
		Musculoskeletal
		Joint involvement (6)
		Renal
		Proteinuria > 0.5 g/24 h (4)
		Renal biopsy class II or V (8)
		Renal biopsy class III or IV (10)
		Immunology domain
		Antiphospholipid antibodies
		Anti-cardiolipin OR anti-B2GP1 antibodies OR lupus anticoagulant (2)
		Complement proteins
		Low C3 OR low C4 (3)
		Low C3 AND low C4 (4)
		SLE-specific antibodies
		Anti-dsDNA antibody OR anti-Smith antibody (6)

Table 2.
Criteria for SLE diagnosis based on different criteria.

glomerulosclerosis). Importantly, biopsy findings should be interpreted and correlated carefully with patients' clinical features and serology.

In an analysis by *Ishizaki et al.* of 48 SLE patients who had renal biopsies but no urine abnormality, 36 patients were identified to have some morphologic changes. Although majority had class I/II (72%), six (17%) patients were found to have class III/IV LN [60]. LN has characteristic histological features that differ from other glomerular pathology and may involve lesions in the glomerular, vascular or tubulointerstitial structures. Analysis of 860 renal biopsies by *Kudose S et al.* confirmed 5 histopathological features of LN; 1) "full-house" staining by immunofluorescence (IF) 2) intense C1q staining 3) extraglomerular deposits 4) combined subendothelial and subepithelial deposits and 5) endothelial tubuloreticular inclusion [61].

The first published classification of glomerular changes in LN was formulated in 1974 under the auspices of the World Health Organisation (WHO; **Table 3**). It divides glomerular changes into five classes, which became the basis of today's classification. Class I applies to biopsies with no detectable changes in glomeruli; class II for pure mesangial disease, class III and IV were defined as proliferative disease, with the former affecting <50% of glomeruli and latter >50%. Class V was for membranous changes. This was modified in 1982, which include replacement of "focal proliferative" term to "focal segmental" GN and addition of a new category, class VI, which denoted advanced sclerosing GN (**Table 3**) [62].

Due to inconsistencies and ambiguities of the available classification criteria, under the auspices of International Society of Nephrology/Renal Pathology Society (ISN/RPS), a new classification of LN was proposed in 2003 [63]. While keeping the overall architecture of the 6 classes in LN, several significant changes were made and emphasis was given to standardisation of biopsy reports. Definition of class I was changed to normal glomeruli under light microscopy but with mesangial deposits under IF. There was also subdivision of class IV into diffuse segmental (IV-S) or diffuse global (IV-G), while terms active (A), chronic (C) or acute-on-chronic (A/C) lesions were also introduced.

The ISN/RPS classification for LN was revised in 2018; among the changes include elimination of the subdivisions of class IV into segmental (IV-S) or global (IV-G), replacement of previous denomination of active (A) and chronic (C) to the actual activity indices (maximum score for activity index is 24 and chronicity index is 12; **Table 4**), and preference for the term "hypercellularity" rather than "proliferation" [64]. The lack of classification for tubulointerstitial and vascular involvement in LN will be addressed and revised after the next (phase 2) international nephropathology working group evaluation and recommendations [64].

WHO 1974	**ISN/RPS 2003**	**ISN/RPS 2018**
Class I Normal glomeruli	*Class I* Minimal mesangial lupus nephritis	*Class I* Minimal mesangial lupus nephritis [d]
Class II Pure mesangial alteration	*Class II* Mesangial proliferative lupus nephritis	*Class II* Mesangial proliferative lupus nephritis [d]
Class III Focal proliferative glomerulonephritis	*Class III* Focal lupus nephritis [a, b]	*Class III* Focal lupus nephritis [d]
Class IV Diffuse proliferative glomerulonephritis	*Class IV* Diffuse segmental (IV-S) or global (IV-G) lupus nephritis [a, b]	*Class IV* Diffuse lupus nephritis [d]
Class V Membranous glomerulonephritis	*Class V* Membranous lupus nephritis [c]	*Class V* Membranous lupus nephritis [c, d]
	Class VI Advanced sclerosing lupus nephritis	*Class VI* Advanced sclerosing lupus nephritis [d]

WHO: World Health Organisation;* **ISN/RPS*: International Society of Nephrology/Renal Pathology Society;* **a***: indicate the proportion of glomeruli with active and sclerotic lesions;* **b***: indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents;* **c***: may occur in combination with class III or IV;* **d***: activity and chronicity indices (total scores of 24 for activity, 12 for chronicity).*

Table 3.
Lupus nephritis classification.

Items	Score	Comment
Activity Index		
Endocapillary hypercellularity	0 to 3+	0 to 3+ based on % involvement of glomeruli or tubulointerstitium. 0 = none, 1+ = <25%, 2+ = 25–50%, 3+ = > 50%.
Neutrophils/karyorrhexis	0 to 3+	
Fribrinoid necrosis	0 to 3+ (x2)	
Hyaline deposits	0 to 3+	
Cellular/fibrocellular crescents	0 to 3+ (x2)	Double weightage for fibrinoid necrosis and cellular/fibrocellular crescent.
Interstitial inflammation	0 to 3+	
TOTAL	24	
Chronicity Index		
Total glomerulosclerosis score	0 to 3+	0 to 3+ based on % involvement of glomeruli or tubulointerstitium. 0 = none, 1+ = <25%, 2+ = 25–50%, 3+ = > 50%.
Fibrous crescent	0 to 3+	
Tubular atrophy	0 to 3+	
Interstitial fibrosis	0 to 3+	
TOTAL	12	

Table 4.
Modified NIH activity and chronicity scoring system (ISN/RPS 2018).

5. Management

5.1 Current management strategies

Early treatment in LN has been shown to improve outcome; however, effective management remains a challenge. It requires a multidisciplinary team approach (MDT), ideally by rheumatologists, nephrologists and nephropathologists. The cornerstone of treatment entails corticosteroids, antimalarial, and steroid-sparing agents (conventional immunomodulators and/or biological therapies) tailored to individual patients based upon histological class and severity to achieve rapid resolution of inflammation, proteinuria <0.5–0.7 g/day by 12 months (or up to 24 months in baseline nephrotic range proteinuria) [47] and prevention of relapsing episodes.

5.1.1 Induction phase

While there is little agreement for class II LN, in active proliferative class III, IV and pure membranous class V (with nephrotic range proteinuria or proteinuria >1 g/day despite optimal use of renin-angiotensin-aldosterone system (RAAS) blockers), the current recommendation for initial induction treatment options include either low-dose intravenous cyclophosphamide (CYCi; 500 mg fortnightly infusions for 3 months) or mycophenolate mofetil (MMF; 2-3 g/day or mycophenolic acid (MPA) at equivalent dose) [47, 65–68]. This is combined with high-dose pulsed intravenous methylprednisolone followed by oral corticosteroid taper. High-dose CYCi is reserved for patients with severe LN due to its' various unfavourable side effects (mainly severe cytopenias and infection, cystitis, ovarian failure, cervical dysplasia and malignancy).

The use of calcineurin inhibitors (CNIs) namely tacrolimus (TAC) and cyclosporin (Cys) either as monotherapy or as part of a multitarget regimen therapy (with MMF/MPA and glucocorticoid) may have a favourable efficacy to induce remission. Meta-analysis in 2017 which included 45 induction trials of diverse participant background confirmed superior efficacy in induction by multitarget

therapy compared to CYCi [69]; however, safety concern with its long term use mainly of chronic progressive irreversible nephrotoxicity remains an issue [70].

5.1.2 Maintenance phase

In the maintenance phase of treatment where less intensive therapy is required, MMF (1-2 g/day or MPA at equivalent dose) or azathioprine (AZA) are the drugs of choice [47, 71, 72] (with or without low dose <7.5 mg/day corticosteroid), depending on the induction regimen and plan for pregnancy. Hydroxychloroquine (HCQ) is recommended for all LN patients in the absence of contraindications [47]. Due to possible ocular toxicity, the dose should not exceed 5 mg/kg body weight and should be adjusted in patients with renal and liver disease, with regular ophthalmological screening.

5.1.3 Refractory lupus nephritis

Rituximab (RTX), although off-label, is not only indicated in patients refractory to conventional therapy or after great cumulative dose of CYCi, but also in patients of child bearing age [47, 73, 74]. Another B-cell targeting therapy which inhibits BlyS, Belimumab has recently been proven to be beneficial as add-on to the standard of care (SOC) therapy (mainly in the MMF subgroup) with primary efficacy renal response seen by week 24 and sustained through week 104 [75].

It is recommended not to discontinue immunosuppression too early as most renal flares occurs during this period. Treatment withrawal can be considered in patients with sustained complete remission for 3–5 years, with treatment deescalation prior to complete withrawal of therapy [47]. Close monitoring of patients and management of co-morbidities including blood pressure (BP) control, treatment of hyperlipidaemia with statins and proteinuria with RAAS blockers are important, while vaccination against influenza and *Streptococcus pneumoniae* are strongly recommended. Repeat renal biopsy may be considered to guide the duration of maintenance immunotherapy and may be required in patients with incomplete response or recurrent LN flares [47, 65].

5.2 Future novel therapeutic options

Developing more effective treatment strategies in LN remains a priority among clinicians and researchers across the globe; however, major challenges exist in its advancement due to the complex pathophysiology and heterogeneity, which directly impact on clinical trial design and overall outcome. Moreover, most trials are conducted with background therapy, which is difficult to control during the study and its subsequent analysis, as there is no clear definition in the SOC [76]. Notwithstanding this, extensive therapeutic strategies have emerged with wide array of novel treatments to improve patient outcomes. Major trend in current treatment landscape for LN focuses on reduction of steroid use.

There is gathering evidence, especially in more recent times, documenting the successful safe use of Belimumab, a monoclonal antibody (mAb) directed against BlyS as an add-on therapy in LN, especially in patients with low complement levels and high anti-DNA antibodies [75, 77]. It is the first targeted therapy and currently the only biological agent approved specifically for LN. There is also increasing interest in the sequential use of two B-cell targeting agents, RTX and Belimumab in active LN [78, 79] with a phase III trial already underway [80]. The rationale for this approach is due to the hypothesis that their co-administration may enhance depletion of circulating and tissue-resident autoreactive B cells.

Another potent BAFF-inhibitor, Blisibimod, was associated with reduction in steroid use, decreased proteinuria and biomarker responses in a multinational phase III trial [81]. Tabalumab, a selective mAb that neutralises both membrane and soluble BAFF, despite having the same therapeutic class, on the contrary did not yield the expected positive statistical significance results in two phase III studies involving SLE patients; however, only approximately 10% of patients in these studies had renal involvement [82, 83].

Voclosporin, a novel next generation CNIs (an analogue of cyclosporin) with enhanced calcineurin inhibition, better safety profile and consistent predictable dose response, despite initial safety concerns in the prior phase II study [84], has recently been demonstrated in a phase III trial to be highly effective for treatment of LN when combined with MMF, with acceptable safety profile, at least for the short term (52 weeks) [85]. More importantly, it has just received the approval by the United States' Food and Drug Administration (FDA) on the 22nd of January 2021, making it the only second targeted therapy approved specifically for LN [86].

There is emerging theoretical evidence for targeting autoantibody-secreting long-lived plasma cells (PCs) that recide in dedicated survival niches in the bone marrow or inflammed tissues of LN patients. Bortezomib, a proteasome inhibitor has been shown to be effective in both animal models and real-world setting but is limited by treatment related toxicity [87–89]. Recently, Ostendorf and colleagues have demosntrated succesful use of Daratumumab, a mAb that targets CD38 and depletes PCs with acceptable safety profile in a patient with refractory LN [90]. The experience of its use however is still limited and more data will be required.

Obinutuzumab, a novel anti-CD20 mAb demonstrated encouraging sustained 18-months B-cell depletion and renal response in a phase II trial with further evaluation in phase III trial underway (can be accessed at ClinicalTrials.gov with identification number: NCT04221477) [91]. BI 655064 (anti CD40 mAb; NCT02770170) has recently completed a phase II trial as add-on therapy to SOC treatment in active LN and awaiting evaluation. Other biological agents currently undergoing clinical trials in the treatment of LN include Anifrolumab (Type I IFN receptor mAb; NCT02547922) in phase II, while Dapirolizumab (pegylated anti CD40 ligand; NCT04294667) and Secukinumab (anti-IL-17 mAb; NCT04181762) are both in phase III trials [92].

A pipeline of novel agents in LN are being developed or asssesed in clinical trials including Ravulizumab (novel anti complement C5 antibody; NCT04564339), Guselkumab (IL-23 inhibitor; NCT04376827), Itolizumab, (anti CD6 antibody; NCT04128579), KZR-616 (proteasome inhibitor; NCT03393013), Iguratimod (novel small molecule; NCT02936375), and BMS-986165 (novel tyrosine kinase 2 (TYK2) inhibitor; NCT03943147) among many others [92].

Targeting the JAK/STAT signalling pathway with Tofacitinib, or CP-690, 550 have been shown to be effective in murine LN model and may potentially serve as therapeutic target in LN [93, 94]. Successful Bruton's Tyrosine Kinase (BTK) inhibition in several studies involving mice LN models supports *Kong et al.* finding of significantly upregulated BTK expression in glomerulus of LN patients and may potentially be a therapeutic target in LN [95–97].

Despite looking promising in SLE, a placebo-controlled phase II/III study to evaluate Atacicept (recombinant fusion protein that inhibits BAFF/BLyS or APRIL) in combination with MMF and corticosteroids in active LN patients was prematurely terminated due to unexpected substantial decline in serum IgG and serious pneumonia infections in Atacicept-treated patients [98, 99]. Abatacept, a recombinant fusion protein co-stimulation modulator, trialled as add on to SOC in LN failed the primary end point of a phase III trial despite demonstarating more rapid reduction of proteinuria and earlier sustained remission [100].

Newer treatment paradigms showing promising results include succesful use of autologous haematopoietic and allogeneic mesenchymal stem cell transplantations for LN in animal studies and among Asian patients [101–106] while *Yu et al.* demonstrated in vitro the protective role by vitamin D in podocyte injury induced by autoantibodies from patients with LN and suggested possible role of vitamin D as a novel therapy target in LN [107].

6. Special considerations

6.1 Pregnancy and lupus nephritis

6.1.1 Pre-pregnancy

Women of childbearing age with LN should understand and be counselled about the potential risks of pregnancy, even if she is in complete remission. Age, previous pregnancy complication, duration from last LN relapse, medication exposure, treatment adherence, blood pressure (BP) control and current disease status are among the important factors that may determine the outcome of future pregnancy. Baseline complement levels, antibody status for dsDNA, SS-A and SS-B, presence of antiphospholipid antibodies (aPL; notably lupus anticoagulant antibody) and urinalysis for proteinuria should be obtained prior to pregnancy.

Possible maternal complications include flare of nephritis, uncontrolled hypertension, pre-eclampsia, risk of Caesarean section, worsening renal function and thrombosis. Foetal risks include prematurity, growth retardation, congenital heart block and intrauterine death [108]. Patients with active disease at conception, uncontrolled hypertension, proteinuria of >1 g/day and abnormal renal function have the highest risk for complications; therefore, good control of disease prior to pregnancy is critically important to optimise pregnancy outcome and ideally the pregnancy should be planned.

Patients on MMF should be transitioned to pregnancy-safe immunosuppressive drugs such as AZA or TAC, while HCQ should be continued throughout pregnancy. MMF exposure especially after the first trimester increases the risk of miscarriage and congenital malformation [109], and practically should be stopped at least 3–6 months prior to conception to ensure disease control is maintained with the new agent(s) [47]. CYC is also teratogenic, associated with premature ovarian failure and increases miscarriage rate [110].

RAAS blockers should ideally be stopped before conception due to possible teratogenicity risk [111]; however, later publications seemed to suggest that they may be safe to be used until pregnancy is confirmed [112]. This is important especially for those who have residual proteinuria as attempt to conceive may take months or even years of effort. Stopping RAAS blockers early on in these patients would essentially exclude them from its' benefits.

6.1.2 During pregnancy

Multidisciplinary team approach is important during pregnancy and should ideally involve the obstetrician, neonatologist, nephrologist and rheumatologist. Majority of patients (80%) with quiescent LN would have successful pregnancies [113]; however, about a third may relapse during pregnancy [108]. Identification of patients who are at higher risk is important when pregnancy begins, as these patients will require closer observation to ensure good maternal and foetal outcomes (**Table 5**) [109, 114–118].

Baseline risk assessment	Possible complication
Active disease during conception	Pregnancy loss, pre-eclampsia, IUGR, prematurity [114]
Proteinuria >1 g/day	Worsening renal function, pre-eclampsia [115]
Uncontrolled hypertension	Pregnancy loss, IUGR, prematurity, pre-eclampsia [114]
Presence of SS-A antibody	Neonatal lupus (congenital heart block) [116]
History of recent acute kidney injury	Pre-eclampsia, IUGR and prematurity [117]
Chronic kidney disease	Worsening renal function, prematurity, IUGR, preeclampsia [118]
Mycophenolate exposure during pregnancy	Miscarriage and embryopathy involving ear, mouth, finger and ocular malformation [109]

**IUGR: Intra-uterine growth retardation.*

Table 5.
Baseline risk assessment during pregnancy.

During early pregnancy, BP would usually remain normal even in patients who required antihypertensive before pregnancy. Gradually, BP may rise as pregnancy progresses, requiring reintroduction of hypertensive medications such as labetalol, methyldopa or nifedipine. BP control should be targeted to be less than 140/90 mmHg [119]. As these patients are at higher risk to develop pre-eclampsia, high dose calcium supplementation and aspirin should be prescribed before entering 16 weeks of gestation [120, 121]. Ultrasound screening including uterine and umbilical artery Doppler to detect early signs of placental insufficiency may be performed at regular interval, especially in high-risk patients.

Hydroxychloroquine is safe during pregnancy and discontinuation has been associated with lupus flare. It also significantly reduces the risk of foetal congenital heart block in patients with positive SS-A (anti-Ro) [116]. Other drugs for consideration in LN and compatible with pregnancy include AZA, CNIs (TAC, Cys), plasma exchange and intravenous immunoglobulins. Data on RTX in pregnancy is limited, although some clinicians have used it safely in early trimester without apparent complication [122]. LN flare during pregnancy can be treated with drugs mentioned above and with addition or increased dosage of steroid. Pulsed intravenous methylprednisolone may be given during severe flares, followed by oral prednisolone [114]. While use of steroid is associated with elevated BP and new onset diabetes, it is probably not related to cleft lip and palate as previously thought [123, 124] (**Table 6**).

Medication	Pregnancy	Breastfeeding
Cyclophosphamide	Increased risk of teratogenicity, especially in 1st trimester	May cause infants' bone marrow suppression
Mycophenolate	Increased risk of congenital malformation and miscarriage	Limited data, not recommended
Azathioprine	Relatively safe. Alternative to mycophenolate	Relatively safe
Hydroxychloroquine	Relatively safe. Improve outcome in antiphospholipid syndrome	Relatively safe
Glucocorticoids	Increase risk of hypertension, preeclampsia, GDM. May have neutral effect on cleft lip and palate	Relatively safe
Calcineurin inhibitor	Increase risk of high blood pressure and diabetes. Relatively safe	Relatively safe
Rituximab	Limited data. No teratogenic effect in animal. 1st trimester use may be possible.	Limited data
Immunoglobulin	Safe in pregnancy. Headache & rash common side effect	Relatively safe

**GDM: Gestational diabetes mellitus.*

Table 6.
Summary of immunosuppressive drugs during perinatal period.

Differentiating between pre-eclampsia and LN flare in pregnancy may be difficult, especially after 20 weeks gestation. Features like proteinuria, high BP, thrombocytopenia and renal impairment are common in both conditions. Red cell cast in urine, abnormal level of complements and anti-dsDNA may point toward LN flare [125]. Elevated soluble fms-like tyrosine kinase 1 (sFlt1)/placental growth factor (PlGF) ratio may assist in predicting pre-eclampsia [126, 127] although not commonly available in clinical practice.

Renal biopsy may be required during pregnancy but poses increased risk of complications. In a systematic review involving data on renal biopsies performed during pregnancy, overall complication rate was higher at 7%, compared to 1% when performed post-partum. Importantly, 4 biopsies during pregnancy had major bleeding complications that required blood transfusion, with median gestational age of 25 weeks; hence, biopsy should only be considered early during the course of pregnancy when results may lead to changes in therapy. Biopsy should be considered if LN flare is suspected and to distinguish it from pre-eclampsia, with finding of glomerular endotheliosis would suggest the latter [128].

Multidisciplinary team approach and patients' engagement are prudent during severe LN flare, as pregnancy termination may be considered with risks and benefits weighed carefully, so that patient can be treated with urgent cytotoxic drugs. Overall rate for preterm delivery and Caesarean section are higher in patients with LN. For patients with non-active disease, delivery at term should be aimed. In those likely to deliver prematurely, dexamethasone should be given to accelerate foetal lung maturation. Delivery should be aimed after 34 weeks to minimise neonatal adverse outcomes; nonetheless, this strategy relies on the overall clinical picture. Timing of delivery is determined by usual obstetric indications and risk of renal deterioration. Mode of delivery does not seem to affect maternal renal function and again should be based on the usual indications accordingly [129].

6.1.3 After pregnancy

The WHO recommends breastfeeding for all babies until 6 months of age, even in patients on immunosuppressive therapy. Although studies found trace amount of immunosuppressives excreted into breast milk, the amount absorbed by infant is negligible and do not exert any clinical effect [130]. Hence, immunosuppressives deemed safe during pregnancy such as corticosteroid, AZA and CNIs can be safely taken during breastfeeding [114]. Post-partum, regular antihypertensive drugs such as amlodipine or bisoprolol can be reinstated and RAAS blockers such as enalapril or captopril can be safely used during breastfeeding [131] (**Table 6**).

Postpartum risk of thromboembolic disease increases in SLE especially in active LN patients with nephrotic-range proteinuria. Preventative measure with heparin during postpartum period is controversial, but may be considered in active LN patients with risk factors such as advanced age, obesity, Caesarean section delivery, and pre-eclampsia [132]. For patients with chronic kidney disease and significant proteinuria during pregnancy, careful monitoring after delivery is required as decline in renal function may accelerate within 6–12 months postpartum, despite having stable renal function during pregnancy [133].

6.2 Renal transplantation in lupus nephritis

Approximately 10–20% of patients with LN will progress to ESRD, with young female of African ancestry having the highest risk [8, 134]. In general, outcome for renal transplant is better compared to dialysis particularly with preemptive transplantation, including in patients with LN [135]. However, many patients

may not be in complete remission despite dialysis initiation, making preemptive transplantation difficult. Current guidelines suggest that clinical lupus activity and ideally, serologically should be quiescent for 6 months and on no or minimal immunosuppression prior to transplantation [47, 136]. Even if on dialysis, the waiting time for transplant should be maximally shortened to reduce potential risk of graft failure [137].

Although the benefit of transplantation is clear, earlier studies have suggested that LN patients may have worse survival outcome compared to ESRD patients of other aetiologies; however, more contemporary studies seem to abrogate this finding [138]. Clinically relevant recurrence rate of SLE post transplantation is less than 5%, but it increases the risk of graft failure [136]. The rate may even be higher if electron microscopy finding is included and protocol biopsy implemented; nevertheless, the lower rate is probably due to the similar immunosuppressive therapy used in both transplant recipient and active LN.

During pre-transplant evaluation, particular attention should be given to screening of aPL as its' presence increases the risk of graft thrombosis. Patients with APS would require careful consideration of perioperative anticoagulation to prevent graft loss. Presence of anti-dsDNA or low complement level is not a predictor for renal transplant outcomes. SLE patients have higher risk for cardiovascular mortality hence will require careful cardiac evaluation prior to transplantation [138]. Recurrence of LN after transplantation can be treated by increasing the dose of the immunosuppressive drugs already being used post transplant. CYC may be considered in severe or aggressive disease while RTX has been used in resistant cases [139].

There is concern in LN patients of having higher risk to develop cancer with prolonged exposure to immunosuppression. Previous exposure to CYC doubles the risk for cancer post transplantation, primarily of the skin [140]. Prior use of immunosuppressive therapies before transplant also increases the risk for non-Hodgkin's lymphoma, anogenital, breast, renal and bladder cancers [141, 142]. Furthermore, prolonged corticosteroid exposure in transplanted SLE patients should adhere to the screening and treatment recommendations on bone health [143].

7. Conclusion

Emerging insights into the heterogenous immunopathogenesis of LN have lead to novel, tailored therapeutic options, resulting in significantly better disease control and prolonged remission among patients; nonetheless, more in-depth studies are required to better understand the pathogenesis while novel therapies continue to be tested. The advent of signature biomarkers show promise in diagnosis, evaluation and management of LN and will continue to be validated for meaningful real-world application. Timely diagnosis, prompt treat-to-target treatment, MDT approach and adherence to therapy are important factors to preserve renal function, prevent disease progression and significantly improve patients' overall outcome.

Better understanding of disease pathways and discoveries with subsequent validation of biomarkers will provide opportunity for improvement in early detection, prognostic and disease severity prediction, subgroups stratification, treatment adherence assessment, and decision for best treatment option in a timely manner. Studies targeting a single organ or specific subgroup with similar disease severity, duration and background SOC therapy will assist in better assesment of drug effectiveness and accelerate drug development in LN.

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