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Primer

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Lupus nephritis

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Abstract

Lupus nephritis (LN) is a type of glomerulonephritis and one of the most serious complications of systemic lupus erythematosus (SLE). LN affects 25–60% of patients with SLE, with incidence and prevalence varying by age, sex, ethnicity and socioeconomic factors. LN predominantly develops within 5 years of an SLE diagnosis and, for many patients, it is the initial manifestation that leads to the recognition of SLE. In some patients, LN may develop late in the disease course, highlighting the importance of persistent awareness of its symptoms and signs. Despite an increasing understanding of disease biology and more effective treatment options, LN remains a substantial cause of morbidity and mortality as it can lead to irreversible kidney failure and associated complications. Risk factors for progression to kidney failure include persistent proteinuria, low glomerular filtration rate, hypertension at diagnosis and frequent disease flares. LN pathogenesis involves complex immune dysregulation, with key pathways including type I interferon signalling, calcineurin activation, and B and T cell dysfunction. Several immunomodulatory drugs are used for the management of LN, and treatment paradigms are increasingly shifting towards multi-agent regimens. Along with appropriate pharmacotherapy, multidisciplinary care tailored to the patient's individual needs, involving rheumatologists, nephrologists, social workers and other health professionals, is crucial for holistically addressing both the immune and non-immune risk factors for progressive kidney function loss and for maximizing kidney lifespan in LN.

Sections

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Introduction

Lupus nephritis (LN) is a complex immune-mediated glomerulonephritis that occurs in patients with systemic lupus erythematosus (SLE). SLE is an autoimmune disease characterized by a loss of tolerance against numerous autoantigens (most notably DNA, ribonucleoproteins, nucleosomes and histones), leading to systemic inflammation and immune-mediated injury in multiple organs[1–3]. Despite an increasing understanding of disease biology and more effective treatment options, LN remains a substantial cause of morbidity and mortality among patients with SLE, primarily because active LN can lead to irreversible chronic kidney disease (CKD) and its associated complications. Repeated episodes of active LN are the most important cause for the progression of CKD to kidney failure requiring kidney replacement therapy, also referred to in the literature as end-stage kidney disease (ESKD)[3].

Controlling active LN requires potent immunosuppressive drugs, such as glucocorticoids to suppress kidney inflammation and cyclophosphamide or mycophenolate mofetil (MMF) to control autoreactive lymphocytes in the lymphoid tissues. Adding B cell-targeting therapies or calcineurin inhibitors can result in increased frequencies of complete responses and a faster treatment response. B cell-targeting therapies seem to reduce the number of subsequent LN flares and slow the decline in kidney function over time. However, important management challenges remain. These include defining disease endotypes and matching these endotypes to specific treatments; reducing drug non-adherence; differentiating persistent immunological activity from chronic, irreversible damage during follow-up; and limiting drug toxicity[4–7].

In this Primer, we summarize the epidemiology of LN; the disease pathobiology; and screening, diagnostic, management and monitoring approaches, and consider how LN and its treatment affect patient quality of life. We also provide recommendations on how to improve long-term kidney and systemic outcomes in patients with LN.

Epidemiology

Prevalence, incidence and mortality

LN is the most common severe manifestation of SLE, affecting 25–60% of patients[1,8]. LN may be present at the time of SLE diagnosis and, if not, usually occurs within the first 5 years of diagnosis. However, studies with over four decades of follow-up have shown that LN may occasionally develop late during the disease course, in some patients more than 10 years after the onset of SLE[9,10].

The prevalence and incidence of LN vary by age, sex, ethnicity/race and the criteria used for diagnosis in different cohorts (for example, sole use of clinical manifestations versus incorporation of histological information). The prevalence of LN is higher among patients with childhood onset than among those with adult-onset SLE, particularly among male and non-white children[11]: 36–55% of patients with childhood-onset SLE develop LN, most commonly within the first year of diagnosis[12]. Although prognosis has improved over time, studies from various geographic regions show that 5–20% of children with LN develop kidney failure during the disease course[13].

In an international inception SLE cohort, LN occurred in 38% of adult patients[14]. The overall prevalence of LN in the United States Medicaid beneficiary population from 2000 to 2004 was 30.9 per 100,000 adults[15]. In a cohort based in Olmsted County, Minnesota, a modest increase in the estimated LN prevalence, but similar incidence rates, were reported between 1985 and 2015 (ref. 16). SLE occurs more frequently in women than in men (general estimate 9:1), but the proportion varies between ethnic or ancestral groups[1]. Similarly, the prevalence and incidence of LN are higher in women than in men[16], but these differences decrease with age[17]. Whether men have a more severe LN course remains controversial owing to conflicting reports, partly attributed to variations in study populations (for example, incident versus prevalent LN) and the overall low numbers of male patients[18,19].

LN is more common and usually has a more severe course in non-white individuals and in those with low socioeconomic status[15]. The prevalence of LN is higher in Black (34–51%), Hispanic (31–43%) and Asian (33–55%) patients with SLE than in white (13–23%) individuals[20]. Little is known about the prevalence and incidence of LN in Africa and in Australasia/Oceania[21]. African Americans with LN have a twofold higher incidence of ESKD, lower likelihood of kidney transplantation and higher mortality risk than white patients with LN[22]. Differences across racial and ethnic groups have been associated with genetic, environmental and socioeconomic factors[20,23,24]. The apolipoprotein L1 gene (*APOL1*) nephropathy risk alleles G1/G2 are more prevalent in Black than in white individuals (26% versus <1%) and are associated with a higher risk of and shorter time to kidney failure development[25].

In a meta-analysis of studies from both developed and developing countries published between 1971 and 2015, 22% of patients overall and 44% of those with diffuse class IV LN involving ≥50% of the glomeruli developed ESKD over 15 years. The risk of kidney failure in LN steadily improved from the 1970s to the mid-1990s, followed by a plateau and then a slight increase in the late 2000s (ref. 26). Risk factors for the development of kidney failure include proteinuria, low glomerular filtration rate (GFR) and hypertension at diagnosis, failure to achieve complete response during the first year of treatment and frequent disease flares[27]. Among patients with LN and kidney failure, African Americans, especially those <40 years of age, have a higher mortality risk than white individuals[28].

Kidney involvement is associated with increased mortality in patients with SLE (standardized mortality ratio: 7.9; 95% CI 5.5–11.0)[29], which varies widely depending on the severity of kidney involvement, response to treatment and the presence of comorbidities. Kidney failure, infections and cardiovascular events are the leading causes of death in patients with LN[30,31]. After a period of major improvement following the establishment of intravenous cyclophosphamide and MMF to induce remission, survival in SLE and LN seems to have plateaued, possibly reflecting the limitations of current treatment strategies, failure of several phase III clinical trials of new therapeutic modalities despite promising results in phase II trials[32], delays in initiating treatment, hindered access to care in many countries and poor adherence to medications[16,30].

Genetic and environmental risk factors

Both genes and the environment have been implicated as risk factors for SLE and LN. At least 180 common genetic variants, each with a low effect size and several with a high effect size contribute to SLE susceptibility[33–35]. Several of these gene variants are associated not only with SLE but also with LN, including alterations in genes that affect lymphocyte activation (*BLK*, *HLADR2/DR3*, *IKZF1* and *STAT4*), cell–cell interactions (*ITGAM* and *TNFSF4*), immune complex handling (*FCGR2A*), type I interferon activation (*IRF5*, *IRF7* and *IFIH1*), innate immune system/inflammatory signalling (*ITGAM*, *TNFAIP3*, *TNIP1* and *UBE2L3*) and other functional pathways (*KLK1*, *APOL1* and *VANGL1*)[33–35]. Additional reasons for kidney affliction and/or worse kidney outcomes in SLE include genetically predisposed abnormalities of podocytes or the glomerular filtration barrier (for example, collagen IVA3, 4 and 5 variants associated with haematuria) or other nephropathogenic gene variants[36]. Sexual dimorphism in SLE and

LN seems to be driven by hormonal differences coupled with failed inactivation of X chromosome genes, including *TLR7*, *TASL*, *IRAK1* and *TMEM187*, all of which affect interferon and/or inflammation signalling[35].

However, the reported genetic loci explain only ~30% of the susceptibility for SLE[37]. In addition, the concordance rate for SLE among monozygotic twins is <25% (ref. 38). Indeed, there is mounting evidence implicating environmental factors in SLE onset and LN flares, including infections, such as with Epstein–Barr virus (EBV) infection, cigarette smoking, UV radiation, exogenous oestrogens, air pollution, silica dust, other inhaled particulates and lifestyle choices[39,40]. From the available data, no single environmental agent seems to be the dominant trigger; each factor has a modest effect, with hazard ratios in the range of 1.5–2.0. EBV infections and smoking promote disease onset, particularly in patients with specific genotypes[41,42], underscoring the importance of gene–environment interactions. Intriguingly, chromatin immunoprecipitation sequencing studies of B cells reveal that as many as 50% of SLE disease loci have binding sites for the EBV-encoded transcription factor EBV nuclear antigen 2 (ref. 43). Thus, when a person with SLE-associated genes is exposed to the EBV virus, viral-derived proteins can directly upregulate these genes, leading to disease.

Both genetic and environmental factors can influence gene expression, for example, through epigenetic modifications, including DNA methylation and histone modification. An epigenome-wide association study of whole-blood DNA methylation profiling in patients with SLE implicates the IFN pathway, antigen processing, HLA class I presentation, cytokine signalling and altered transcription factor binding[44]. These changes were associated with distinct molecular subtypes of the disease and highlight opportunities for new therapeutic intervention. Similar studies examining the inflamed kidneys in patients with LN are eagerly anticipated.

Mechanisms/pathophysiology

The activation of multiple adaptive and innate immune cells in the periphery leads to systemic autoimmunity in SLE, marked by the production of autoantibodies against double-stranded DNA (dsDNA) and other nuclear antigens, and the formation of immune complexes[45]. The deposition of autoantibodies and immune complexes within the kidneys leads to inflammation, which is clinically diagnosed as LN. In addition, both adaptive and innate immune cells from the periphery can infiltrate the kidneys, further contributing to tissue injury. Indeed, immune aggregates resembling lymphoid structures can be found within LN kidneys and are associated with poor outcome in LN[46].

Key functional pathways

Among the multitude of functional pathways activated in immune cells from patients with SLE and LN, perhaps the most studied and reproduced pathway is the type I interferon axis, commonly referred to as the type I interferon (IFN-I) signature. In SLE and LN, cellular and serum IFN-I levels are elevated, probably caused by the increased availability of nucleic acids that can stimulate cytosolic and endosomal nucleic acid sensors in individuals with genetic polymorphisms that amplify responsiveness to these nucleic acids and downstream interferon production (Box 1). This activation is associated with the earlier development of nephritis, proliferative LN in particular, both systemic and renal disease activity, and poor response to treatment[45,47,48]. Glomerular and tubular IFN-I signatures have been reported, with the latter correlating with proteinuria and high kidney pathology chronicity index scores[45]. This pathway continues to be an important therapeutic target owing to its commanding role in immune and resident renal cells (Fig. 1).

Box 1 | What causes the heightened interferon signature in lupus nephritis?

Mechanisms behind the interferon signature in lupus nephritis include[33–35,45,57]

- Lupus genes (*DNASE1* and *DNASE1L3*), which may impair enzymes that degrade extracellular DNA.
- Autoantibodies to *DNASE1* and *DNASE1L3* prevent the degradation of extracellular DNA.
- Neutrophil extracellular traps, apoptotic bodies, microparticles and mitochondrial DNA extruded from neutrophils and platelets constitute a rich source of immunostimulatory DNA.
- Accumulating RNA and DNA trigger endosomal nucleic acid sensors, TLR7 and TLR9.
- *TLR7* polymorphisms and failure of X chromosome inactivation increase TLR7 activity.
- Rare mutations (*TREX1*) can activate cytoplasmic nucleic acid sensors (cGAS and STING).
- Activation of endosomal and cytoplasmic nucleic acid sensors promote interferon type I (INF-I) production.
- Lupus genes (*IRF3*, *IRF5*, *IRF7*, *IRF8*, *IFIH1*, *IRAK1*, *ITGAM*, *STAT4* and *TNFAIP3*) further amplify IFN-I signalling in genetically susceptible individuals.

In addition, multiple cell signalling pathways are activated within adaptive and innate immune cells in LN, including the calcium-dependent calcineurin pathway, the AKT–mammalian target of rapamycin (mTOR) pathway, NF-κB signalling and JAK–STAT axis, all constituting attractive nodes for therapeutic intervention[49] (Fig. 1). The calcineurin pathway not only activates B cells and T cells but is also important in podocyte injury as calcineurin dephosphorylates synaptopodin, leading to proteinuria, podocyte loss and, ultimately, glomerulosclerosis[50] (Fig. 2). This observation provides the molecular rationale for using calcineurin inhibitors in LN.

T cells

Genetic variants associated with SLE implicate T cells in disease pathogenesis[33], representing the most prevalent immune cell infiltrate within LN kidneys. Type 1 helper T cells, type 2 helper T cells, follicular helper T cells, T helper 17 cells, CD8 cells and double-negative T cells have all been documented in LN kidneys, both in peri-glomerular margins and in tubulointerstitial regions, with varying associations with disease severity and renal outcome[3,45]. In addition to their key function in activating B cells systemically towards the formation of class-switched age-associated (also known as autoimmunity-associated) B cells (ABCs) (Fig. 1), T cells may also have a role within the renal milieu in activating other immune cells or inflicting podocyte injury, although the detailed mechanisms remain unclear[3,45]. Tissue-resident effector memory T cells have also been documented within LN kidneys[51,52]. Studies have also highlighted the potential pathogenic importance of IL-17-producing double-negative T cells in LN[53,54]. Tertiary lymphoid structures in LN kidneys, comprising $CD8^+$, γδ and double-negative T cells, are associated with acute refractory disease and progression to kidney failure[46]. Taken together, tissue-resident memory T cells, tissue-resident plasma cells and tissue-resident macrophages may constitute smouldering

hot spots of immune activity within the kidneys, repeatedly setting off disease flares. Extinguishing these recalcitrant hot spots is an important goal of future LN therapy.

Neutrophils and macrophages

Common SLE-associated genetic variants also implicate innate immune cells, such as neutrophils and macrophages, in the

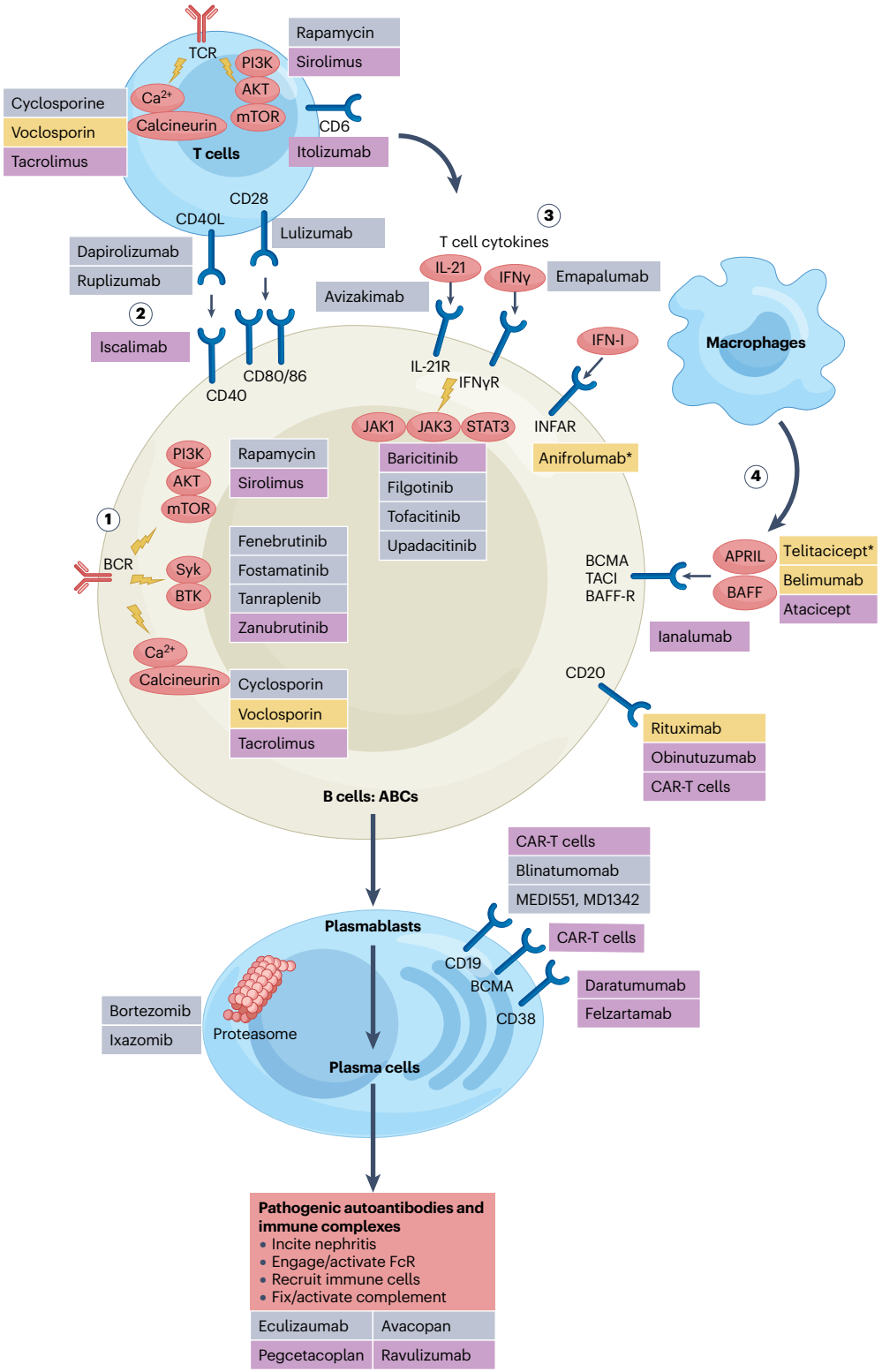

Fig. 1 | Adaptive immune cells involved in LN pathogenesis. The activated memory B cell, termed the age-associated (or autoimmunity-associated) B cell (ABC), is a key cell in lupus nephritis pathogenesis. It is induced by various stimuli: stimulation of the B cell receptor (BCR) by autoantigens (1); T cell help mediated via CD40, CD80, CD86 and other co-receptors (2); cytokine stimulation by interferon-γ (IFNγ), IL-21 and IFNα (3); engagement of the receptors for B cell-activating factor belonging to the tumour necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) on B cells (4); and TLR7 ligation (not shown). Targeting CD19 with chimeric antigen receptor (CAR)-T cells or antibodies may deplete plasmablasts and certain plasma cell subsets. Other plasma cell subsets do not express CD19 or do so at low levels, and these may be eliminated by therapies targeting CD38 or B cell maturation antigen (BCMA). Finally, as autoantibodies incite inflammation by activating the complement system, inhibitors that check complement activation at multiple steps along that pathway are also attractive drug candidates in lupus nephritis. All these pathways can potentially be therapeutically targeted. Approved drugs are shown in yellow boxes (asterisks denote drugs approved for systemic lupus erythematosus, but not for lupus nephritis (LN)). Drugs in previous or ongoing clinical trials of LN are shown in purple boxes (Supplementary Table 1 summarizes drugs in ongoing clinical trials of LN). Other drugs of potential use are shown in grey boxes. FcR, Fc receptor; mTOR, mammalian target of rapamycin; TCR, T cell receptor.

pathogenesis of the disease[33]. Neutrophil-associated peripheral blood transcriptomic signatures are strongly associated with disease activity in LN[55–57]. Increased blood levels of low-density neutrophils, the propensity of these cells to release neutrophil extracellular traps, a rich source of bona-fide SLE autoantigens and the demonstrated pathogenicity of neutrophil extracellular traps in murine LN all allude to the pathogenic potential of low-density neutrophils[58]. However, glucocorticoid use can also augment the circulating levels of these neutrophil subsets, and further analysis of their role in LN pathogenesis is required.

Distinct macrophage subtypes have been documented within LN kidneys, with demonstrated pathogenicity in murine models[3,45]. Patrolling CD16^{hi} monocytes are recruited into inflamed kidneys as CD16^{hi} pro-inflammatory classical (monocyte-derived) macrophages, which then enter a phagocytic phase, and eventually differentiate into non-classical (monocyte-derived) macrophages (M2 type macrophages, with high CD163 expression)[59]. Indeed, the number of glomerular M2-like macrophages correlates with proteinuria in LN[60]. Separate from these monocyte-derived macrophages, tissue-resident macrophages in LN kidneys express B cell-activating factor belonging to the TNF family (BAFF) and other factors that engage and activate B cells, sustaining the growth of ectopic lymphoid aggregates, conducive to in situ plasma cell formation and autoantibody production[60].

Single-cell transcriptomic studies have uncovered a unique subset of monocytes and macrophages that are expanded within the kidneys at the onset of LN, both in murine models and patients, expressing genes such as *CD9*, *SPP1*, *CTSD*, *CD63*, *APOE* and *TREM2*, constituting gene signatures previously associated with tissue injury and repair[61]. Innate lymphoid cells expressing receptors, such as NKp46, may also be important in activating these macrophages within the kidney milieu by producing GM–CSF[62].

B cells, ABCs, plasma cells and autoantibodies

The importance of B cells in the pathogenesis of SLE and LN is supported by the beneficial effect of B cell-targeting therapies and the current enthusiasm for harnessing B cell-targeting chimeric antigen receptor (CAR)-T and CAR natural killer cells to treat refractory SLE and LN[63–65]. B cell infiltrates have been documented within LN kidneys, most notably in the tubulointerstitium, including germinal centre-like B cells[66]. Importantly, when genes implicated in SLE pathogenesis were imputed for cell types, ABCs and plasma cells emerged as key cell types implicated in disease[33], with similar observations when epigenetic signatures (gene enhancers) were examined[67].

ABCs are CD19^{+}CD21^{-}CD11c^{+} antigen-experienced, class-switched memory B cells that express ITGAM, ITGAX, FcRL5 and TLR7 and receptors for IFNα, INFγ and IL-21[68] (Fig. 1). ABCs are expanded in peripheral blood of patients with SLE, are more numerous in patients of African American ancestry, and are associated with proliferative LN, SLE disease activity and high levels of autoantibodies[69–71]. Importantly, they are also expanded within LN kidneys, correlating with LN disease activity[72,73].

Sustained activation of the B cell receptor by autoantigens, chronic inflammation, and stimulation by IFNγ, IL-21 and TLR7 ligands have all been shown to drive the formation of ABCs in vitro, which readily differentiate into autoantibody-producing plasma cells[33,68–70]. Among the dozens of autoantibodies documented in SLE and LN, antibodies against dsDNA, Smith antigens (Sm) and nucleosomes are well documented in terms of pathogenesis and/or disease diagnostics[3,45]. Indeed, eluates from the kidneys of patients with proliferative LN are enriched for antibodies against dsDNA, C1q, Sm, SSA, SSB and chromatin[74]. The likely direct involvement of autoantibodies in binding renal antigens and inducing disease has been demonstrated in adoptive transfer studies using both murine and human anti-DNA antibodies[75,76]. Direct binding to antigenic targets within the kidneys, for example, kidney-resident nucleosomes, vimentin and α-actinin[77,78], and

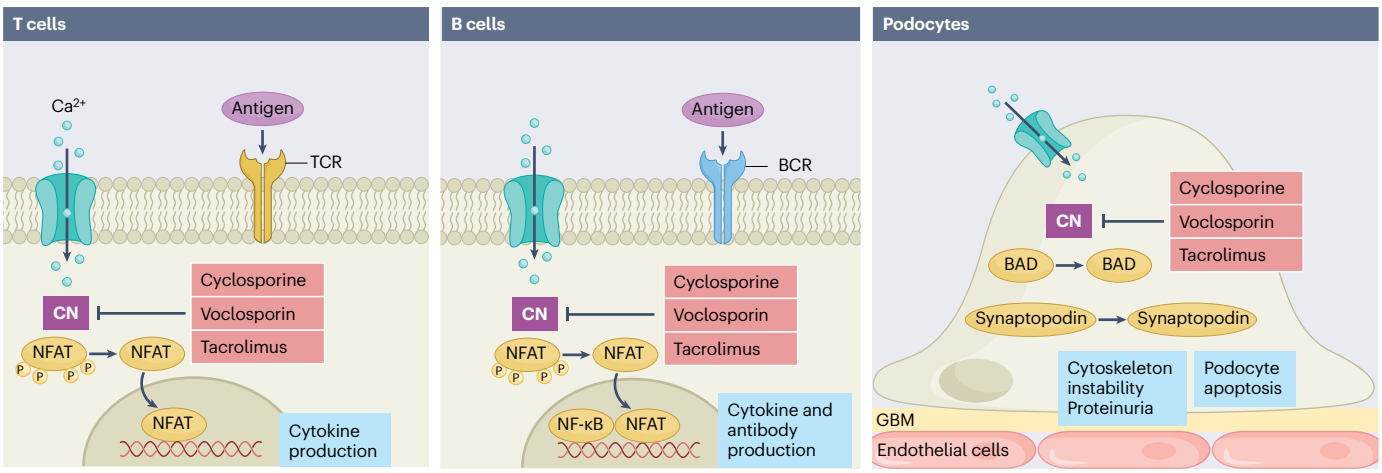

Fig. 2 | Calcineurin inhibitors target shared signalling pathways in lymphocytes and podocytes. Calcium flux into the cell activates calcineurin (CN), a Ca^{2+}-sensitive phosphatase that dephosphorylates different substrates in different cells, leading to diverse consequences. In T lymphocytes and B lymphocytes, antigen recognition by the T cell receptor (TCR) and the B cell receptor (BCR) leads to activation of nuclear factor of activated T cell (NFAT). This in turn leads to cytokine production by T cells and B cells, and autoantibody production by plasma cells that arise from the B cells (or age-associated (or autoimmunity-associated) B cells (ABCs)). In podocytes, CN dephosphorylates synaptopodin, which regulates actin cytoskeleton stability, leading to proteinuria, podocyte loss and, ultimately, glomerulosclerosis. Similarly, CN dephosphorylates Bcl-2-associated death promoter (BAD), which initiates a cascade of events leading to apoptosis. Importantly, cyclosporine A, tacrolimus and voclosporin all block the phosphatase activity of CN, leading, in effect, to reduced activation and cytokine production by T cells, reduced autoantibody production by B cells, and salvage of podocytes and nephrons. GBM, glomerular basement membrane.

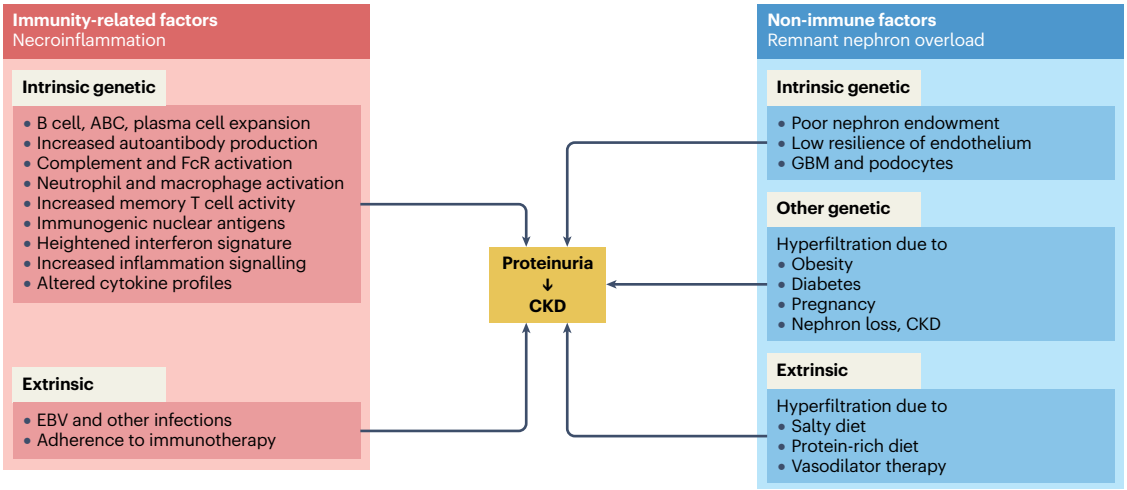

Fig. 3 | Factors leading to proteinuria in lupus nephritis. Immune and non-immune factors contribute to proteinuria in lupus nephritis. Both immune and non-immune mechanisms of proteinuria can be grouped according to genetic and other intrinsic and extrinsic factors. ABC, age-associated (or autoimmunity-associated) B cell; CKD, chronic kidney disease; EBV, Epstein–Barr virus; FcR, Fc receptor; GBM, glomerular basement membrane. Reprinted with permission from ref. 253, Oxford University Press.

pre-formed antigen–antibody immune complexes both engage FcR and complement, leading to the formation of the anaphylatoxins C3a and C5a and the membrane attack complex, which then drive inflammation.

The role of plasma cells in the pathogenesis of LN is also suggested by imputation analysis of both SLE genes and epigenetic signatures[33,67]. Transcriptome-based plasma cell signatures have among the strongest associations with SLE disease activity[79]. Studies in murine lupus reveal that long-lived plasma cells in the bone marrow are important pathogenetic factors, and that these cells can be depleted by proteasome inhibitors but not conventional B cell-depleting therapies or immunosuppressants[80]. Compelling evidence for a plasma cell role in human LN comes from the use of plasma cell-depleting agents[81], such as daratumumab that targets CD38 (ref. 82).

Owing to their central role in mediating the kidney-targeted manifestations of SLE, B cells, ABCs, plasma cell-elaborated autoantibodies and downstream complement system activation are or have been implicated as therapeutic targets in LN. There is less consensus regarding the potential role of other immune cells and resident renal cells in LN pathogenesis[3,45]. The role of immune and non-immune factors in inducing podocyte injury, infringement of the glomerular filtration barrier, crescent formation (a morphological change in the glomerular margins that predicts poor outcome), tubular atrophy and interstitial fibrosis in the context of LN are active areas of investigation.

Development of CKD

Immune complex-mediated activation of Fc receptors and complement system activation drives glomerular inflammation, immune cell recruitment and injury to resident kidney cells[83]. Clinically detectable proteinuria results from podocyte injury and an irreversible loss of podocytes implies scarring (glomerulosclerosis) and atrophy of the tubule of the respective nephron, that is, loss of nephrons and replacement by fibrous interstitial matrix and a step-wise reduction of kidney filtration capacity[84]. Proteinuria itself imposes metabolic stress to proximal tubular cells in still-intact nephrons, which tend to detach followed by compensatory hypertrophy of adjacent tubular cells driving tubular cell senescence, tubulointerstitial inflammation and the activation of interstitial fibroblasts[85]. Indeed, repeat kidney biopsies frequently reveal interstitial fibrosis as a sign of irreversible scarring, implying reduced filtration and metabolic capacity, as well as filtration and metabolic overload, of the remaining nephrons (Fig. 3). Even patients with complete clinical response after an episode of LN show these chronic changes in repeat kidney biopsies, indicative of irreversible nephron loss[86]. Hence, consuming kidney functional reserve increases the risk that the kidneys will be unable to accommodate future increases in workload, for example, from weight gain, salty or protein-rich diets, diabetes mellitus or pregnancy, resulting in greater proteinuria and a more rapid loss of kidney function[84].

Repeated episodes of LN are the most important determinant of long-term prognosis as each flare further reduces nephron number and overall kidney capacity. This progressive loss lowers the likelihood of achieving complete or partial response owing to the increasing haemodynamic and metabolic overload placed on the remaining nephrons[87]. Although a healthy kidney can retain good function for ≥90 years without kidney failure, each LN flare curtails this time span by even decades (Fig. 4). The kidney capacity to deal with irreversible damage depends on the presence of other risk factors that either reduce kidney capacity or increase the workload of the remaining nephrons[84,88–90]. Hence, it is required to mitigate further insults, such as a salty or a protein-rich diet, diabetes mellitus, overweight or obesity, or pregnancy, all of which increase the haemodynamic and metabolic workload of the remaining nephrons and can promote further nephron loss[91]. For example, exposure to nephrotoxic agents, including non-steroidal anti-inflammatory drugs, proton-pump inhibitors and tobacco may impose additional kidney injury. Thus, multiple intrinsic and extrinsic, immune and non-immune factors shape the development of proteinuria, nephron loss and progression of CKD in LN (Figs. 3 and 4).

In devising the next generation of therapies for LN, one should be cognizant of two key aspects underlying disease pathogenesis. First, therapy should be aimed at eradicating recalcitrant renal and extra-renal niches of memory lymphocytes and plasma cells.

Second, every patient with LN should receive comprehensive CKD care, which necessitates interdisciplinary management.

Diagnosis, screening and prevention

The clinical presentation of LN ranges from asymptomatic disease (silent LN)[92] to generalized oedema in nephrotic syndrome (proteinuria >3.5 g/24 h) and hypertension as the two cardinal signs of hypervolaemia. Signs of kidney failure occur in acute nephritic syndrome characterized by glomerular inflammation (glomerulonephritis). Common laboratory findings include proteinuria (ranging from mild to nephrotic), haematuria and leukocyturia on urine dip stick analysis, and acanthocyturia (urinary excretion of acanthocytes, which are ring-shaped red blood cells with vesicle-shaped protrusions), red blood cell casts and white blood cell casts in the urinary sediment[93].

According to the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria for SLE[94], kidney involvement is defined as proteinuria > 0.5 g/24 h in a 24-h urine collection or an equivalent spot urine protein-to-creatinine ratio (UPCR), and/or biopsy-proven LN as classified by the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria[95]. The frequently asymptomatic nature of kidney involvement in SLE justifies regular urine testing as a screening method for detecting urinary abnormalities throughout the entire disease course, as LN can also develop late during the course of SLE.

The UPCR of an intended 24-h urine collection that is at least half-complete provides an accurate estimate of proteinuria[96,97]. The UPCR of random daytime voids is increasingly used but can vary widely from that of a timed collection. Examination of urinary sediment is also a part of routine surveillance.

Kidney biopsy

Kidney biopsy is the gold standard for confirming an LN diagnosis and characterizing the LN subtype based on histological patterns. Assessment of biopsy samples enables detection of silent LN[92], determination of the grade of inflammatory activity and chronic damage, and can guide therapeutic management. It can also help to identify conditions that mimic LN, such as infections, drug toxicity and other forms of glomerular injury[98–102].

A kidney biopsy is recommended in patients with persistent proteinuria, especially when levels exceed 0.5 g/24 h and/or when accompanied by other elements of activity in the urinary sediment, that is, the presence of dysmorphic red blood cells, white blood cells and/or cellular casts detectable on microscopic examination. However, biopsy should also be considered if a patient has persistent, isolated haematuria or pyuria after excluding other causes, or kidney failure of unknown cause[93,100,101]. The procedure is typically percutaneous, with precautions taken to minimize bleeding and infection risks, which are infrequent and generally minor[103,104]. However, patients with LN and coexisting antiphospholipid syndrome (APS), positive lupus anticoagulant, and histological evidence of thrombotic microangiopathy or fibrous intimal hyperplasia may be at an increased risk of post-biopsy bleeding[105]. Patients with persistent or worsening proteinuria or deteriorating kidney function despite treatment should be assessed for other causes, including adverse effects of medications,

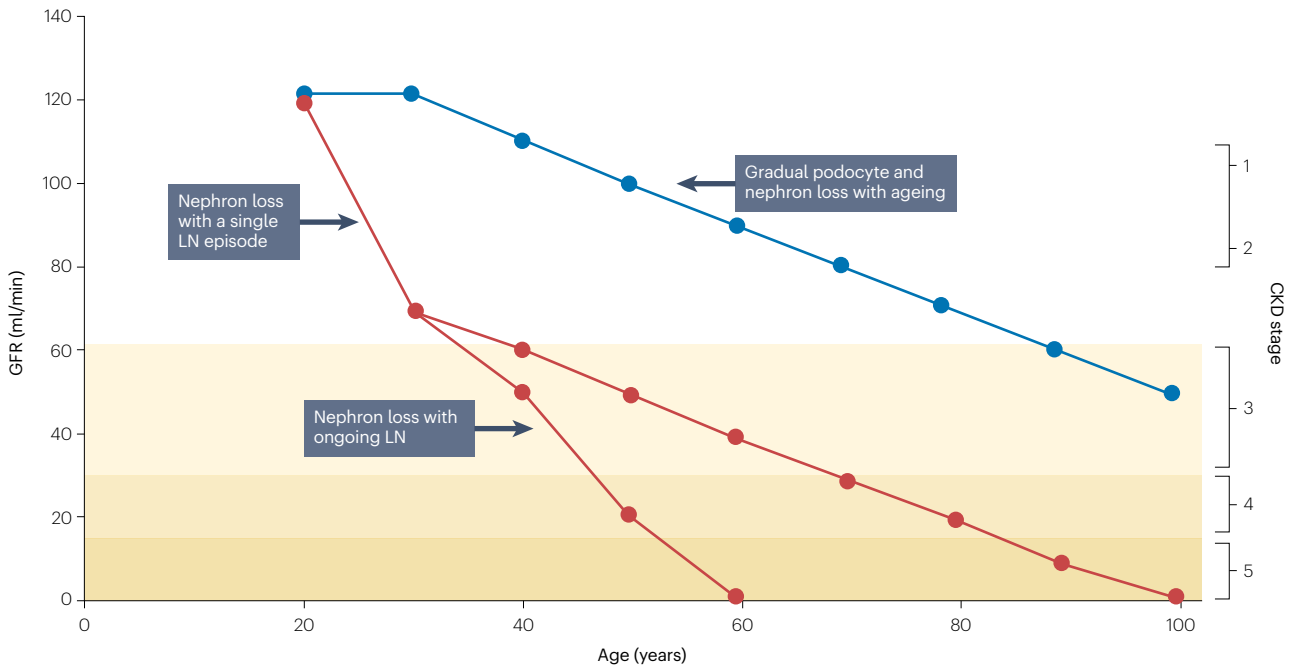

Fig. 4 | Nephron loss as a function of age and renal injury due to LN. Kidney function, assessed by glomerular filtration rate (GFR; left *y* axis), naturally declines with age owing to gradual nephron loss. Kidneys have an average lifespan of ~120 years. This lifespan is reduced in those who were born with fewer nephrons or those in whom nephrons are lost owing to acute kidney injury. In patients with lupus nephritis (LN), each disease flare acts as an acute kidney injury episode, often causing irreversible nephron loss, which considerably shortens the kidney lifespan. Repeated flares further deplete the nephron reserve, accelerating chronic kidney disease (CKD) progression (CKD stage; right *y* axis) and increasing the likelihood of kidney failure that requires replacement therapy. Additionally, persistently active or smouldering LN speeds up nephron loss, leading to earlier onset of kidney failure. Key predictors of CKD progression and kidney failure development in LN include baseline serum creatinine levels, the number of flares and residual disease activity. Adapted with permission from ref. 254, Elsevier.

Box 2 | Proposed nomenclature of repeat kidney biopsy in lupus nephritis

A repeat kidney biopsy can be considered in instances of active serological markers despite clinical response or absence of extra-renal manifestations to assess changes in histological class, residual disease activity and tissue damage. It can also be considered after the initial phase of treatment for treatment evaluation or after long-term clinical remission to assist decisions on treatment tapering. The nomenclature of repeat kidney biopsies performed in routine practice could be stratified according to their clinical indication:

Repeat kidney biopsy at clinical indication
This biopsy is usually performed when there is clinical uncertainty regarding LN status, for example, if clinical activity persists or if serological activity is detected despite clinical quiescence.

Per-protocol repeat kidney biopsy for evaluation of the initial treatment
This biopsy is usually performed around 12 months after commencement of the initial treatment for active disease.

Per-protocol repeat kidney biopsy after long-term clinical remission
This biopsy is usually performed when remission is maintained for at least 12 months to assist decisions on subsequent treatment strategies, including tapering or withdrawal of the immunosuppressive treatment.

renal vein thrombosis, infections, poorly controlled hypertension and non-adherence to treatment.

A repeat kidney biopsy may be considered in patients with active serological markers despite clinical response to assess potential changes in histological class, residual disease activity and chronic lesions due to tissue damage[106]. Importantly, clinical or routine laboratory features of activity and histological activity features in repeat kidney biopsies are often inconsistent, supporting the use of kidney tissue assessment to guide the treatment strategy[107–110]. Thus, repeat kidney biopsies may be performed not only when clinical signs of active LN are present[101] but also after the initial phase of treatment, generally after 1 year, for treatment evaluation[106,111], or after long-term clinical remission for decision on treatment tapering[86,112] (Box 2).

Histological classification

Kidney biopsy samples are examined with light microscopy, immunofluorescence and electron microscopy. Adequate histological information is obtained when ≥10 glomeruli are analysed. LN refers to immune complex-mediated kidney injury, indicated by deposits including IgA, IgG, IgM, C1q, and C3 (ref. 93).

Disease classification is primarily based on glomerular findings[95], but concurrent tubular atrophy, interstitial inflammation and fibrosis, as well as arteriosclerosis and other vascular lesions, for example, thrombotic microangiopathy, should be reported and graded[95,113]. The glomerulocentric nature of current LN classification constitutes a major limitation as it overlooks the crucial roles of the tubulointerstitial compartment regarding disease evolution[114] and prognosis[110].

The 2003 ISN/RPS classification includes six different lesion patterns, referred to as classes[95] (Box 3). Class I refers to minimal mesangial glomerulonephritis. Class II involves mesangial hypercellularity or matrix expansion with mesangial immune deposits. Class III or IV comprises focal or diffuse glomerulonephritis characterized by subendothelial immune deposits. Class V is characterized by subepithelial immune deposits and can co-occur with class II, III or IV. Class VI indicates advanced global sclerosis in ≥90% of the glomeruli.

The description of active and chronic lesions was introduced in 1964 (ref. 115) and refined in 1976 (ref. 116), with a scoring system proposed later[117]. High scores of activity and chronicity based on renal histology are associated with poor kidney prognosis, particularly impending flares (short term) and loss of kidney function (long term), respectively[110,118].

A revision of the ISN/RPS classification in 2018 provided definitions for mesangial hypercellularity and for cellular, fibrocellular and fibrous crescents, replaced the term 'endocapillary proliferation' with 'endocapillary hypercellularity', eliminated the segmental and global subdivisions of class IV, and substituted the A/C designations for active/chronic with modified NIH activity and chronicity indices[113] (Box 3). The interobserver variability with current classification systems remains a concern[119], and the need for a new classification has been highlighted[120]. Distinguishing active from chronic lesions, in particular by non-invasive means, would be clinically highly relevant for guiding the management of LN.

Differential diagnosis

LN is the most common form of kidney involvement in SLE, but histological lesions other than LN may be found in patients with SLE, either alone or along with LN-specific changes. These lesions may have clinical features similar to those of LN but require different management, making accurate histological characterization crucial. Differential diagnoses include thrombotic microangiopathy, interstitial nephritis without glomerular involvement, which may reflect drug toxicity or infections, and lupus podocytopathy, which may present with nephrotic-range proteinuria and responds more readily to glucocorticoids than typical proliferative LN. Additionally, kidney involvement due to comorbid conditions, such as diabetic nephropathy or hypertensive nephrosclerosis may confound the clinical picture, particularly in patients of advanced age, in whom age-related comorbidities are more prevalent, or those with longstanding disease[3].

Thrombotic microangiopathy is characterized by fibrin thrombi in glomerular capillaries and/or arterioles and is present in 6–25% of patients with SLE. APS, thrombotic thrombocytopenic purpura and complement-mediated thrombotic microangiopathy are frequent causes, followed by haemolytic uraemic syndrome, infections, drug use and malignancies[5,121–123]. Within the frame of the 2023 ACR/EULAR classification criteria for APS[123], the terminology of APS nephropathy was re-evaluated to include acute (thrombotic microangiopathy) and chronic lesions (organized arterial or arteriolar microthrombi with or without recanalization, organized glomerular thrombi, fibrous and fibrocellular − arterial or arteriolar − occlusions, focal cortical atrophy with or without thyroidization, and fibrous intimal hyperplasia)[124]. Histological findings of APS nephropathy can coexist with LN[121–127].

The distinct pathophysiology of APS nephropathy[128] and its association with ESKD[125] highlight the importance of histological characterization. The effect of antiphospholipid antibodies on kidney outcomes in LN is unclear, especially in patients without APS nephropathy owing to their heterogeneity and varying pathogenicity[129].

Screening and prevention

Both the first episode of LN and each subsequent relapse increasingly determine kidney outcomes in people with SLE, making early prediction and prompt initiation of treatment crucial. New urine biomarkers for predicting and assessing LN are being explored and independently validated[130,131] but have not yet replaced conventional surveillance markers. Regular screening for LN, typically conducted biannually during quiescent phases and every 1–3 months during active disease, includes evaluation of volume status, blood pressure, urinalysis and serum parameters[4]. Elevation of serum creatinine levels, a new appearance of dysmorphic erythrocytes (acanthocytes in particular) or red blood cell and/or white blood cell casts, and new-onset or worsening of proteinuria may indicate LN onset or flare[132,133]. Importantly, although proteinuria remains a valuable clinical marker of activity in LN, microscopic haematuria has yielded poor prognostic metrics in clinical trial settings[134–136], partially due to considerable interobserver variability[137].

Despite controversy, serum C3 and C4 levels and anti-dsDNA antibody kinetics remain valuable for identifying humoral SLE activity and, therefore, for predicting flares of LN[138,139]. Anti-dsDNA antibody levels typically increase and C3 and C4 levels decrease as SLE activity rises[140]. Young age, low serum C3 levels, high anti-dsDNA antibodies and anti-Sm antibodies at the time of SLE diagnosis increase the risk of developing LN. Other autoantibodies, such as those against C1q and modified C-reactive protein, are associated with LN severity but further investigation is required to assess whether they can be used for screening purposes[141–152]. Positive results for antiphospholipid antibodies, including the lupus anticoagulant, anti-cardiolipin antibodies and anti-β_2-glycoprotein I antibodies, are linked to thrombotic kidney manifestations, such as kidney artery and kidney vein thrombosis and kidney infarcts, in people with SLE and should, therefore, be included in routine screens[123,125,153].

Management

Management principles

Management of LN is based on the extent of inflammation and damage observed in kidney biopsy samples (Fig. 5). Historically, treatment followed a two-step paradigm of induction and maintenance therapy, in which high-intensity regimens are used to induce remission and lower-intensity regimens are used for maintenance. However, clinical practice and trial designs have shifted towards integrated, continuous treatment strategies that blur this traditional separation, reflecting the evolving understanding of disease dynamics and the availability of new therapies.

Primary short-term treatment goals include rapid attainment of remission and minimization of treatment-related toxicity. Long-term goals include prevention of flares, mitigation of CKD progression, preservation of kidney function, and reduction of morbidity and mortality[3,154]. Histopathology findings are a major determinant of treatment choice[106,155]. So far, therapeutic trials have only included patients with proliferative (classes III/IV), membranous (class V) or proliferative plus membranous LN, but not those with class I, II or VI LN. Treatment of patients with an LN class that has been studied in therapeutic trials, especially of those with a proliferative component, should be directed

Box 3 | 2003 ISN/RPS LN classification and scoring for kidney tissue-based LN activity and chronicity

Simplified classification of lupus nephritis (LN) based on the 2023 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification[95].

Class I: mesangial immune complexes only; normal light microscopy.
Class II: mesangial hypercellularity or mesangial matrix expansion with mesangial immune deposits.
Class III: focal glomerulonephritis involving <50% of glomeruli.
Class IV-S: diffuse glomerulonephritis involving ≥50% of glomeruli, with ≥50% of the involved glomeruli showing segmental lesions, that is, lesions involving less than half of the glomerular tuft.
Class IV-G: diffuse glomerulonephritis involving ≥50% of glomeruli, with ≥50% of the involved glomeruli showing global lesions, that is, lesions involving at least half of the glomerular tuft.
Class V: global or segmental continuous granular subepithelial immune deposits.
Class VI: advanced global sclerosis in ≥90% of glomeruli.

Kidney tissue-based LN activity and chronicity

The National Institutes of Health (NIH) activity and chronicity indices evaluate specific morphological components in a kidney biopsy sample. The activity index incorporates six histological features considered measures of active LN, and the chronicity index comprises four histological features that are considered measures of chronic irreversible tissue damage.

Modified NIH activity index[113]

- Glomerular abnormalities
  - Endocapillary hypercellularity (score 0–3)
  - Neutrophils and/or karyorrhexis (score 0–3)
  - Fibrinoid necrosis (score (0–3) × 2)
  - Hyaline deposits (wire loops lesions and/or hyaline thrombi) (score 0–3)
  - Cellular and/or fibrocellular crescents (score (0–3) × 2)
- Tubulointerstitial abnormalities
  - Interstitial inflammation (leukocytes) in the cortex (score 0–3)

Modified NIH chronicity index[113]

- Glomerular abnormalities
  - Global and/or segmental glomerular sclerosis (score 0–3)
  - Fibrous crescents (score 0–3)
- Tubulointerstitial abnormalities
  - Tubular atrophy (in the cortical tubules) (score 0–3)
  - Interstitial fibrosis in the cortex (score 0–3)

Scoring

Each item contributes to the total score with a specific weight: 0, 1 or 3 if present in <25%, 25–50% or >50%, respectively, of the glomeruli; the cortex (interstitial inflammation and interstitial fibrosis); or the cortical tubules (tubular atrophy). The weights of fibrinoid necrosis and cellular/fibrocellular crescents are multiplied by two. The maximum score for the modified NIH activity index is 24, and the maximum score for the modified NIH chronicity index is 12.

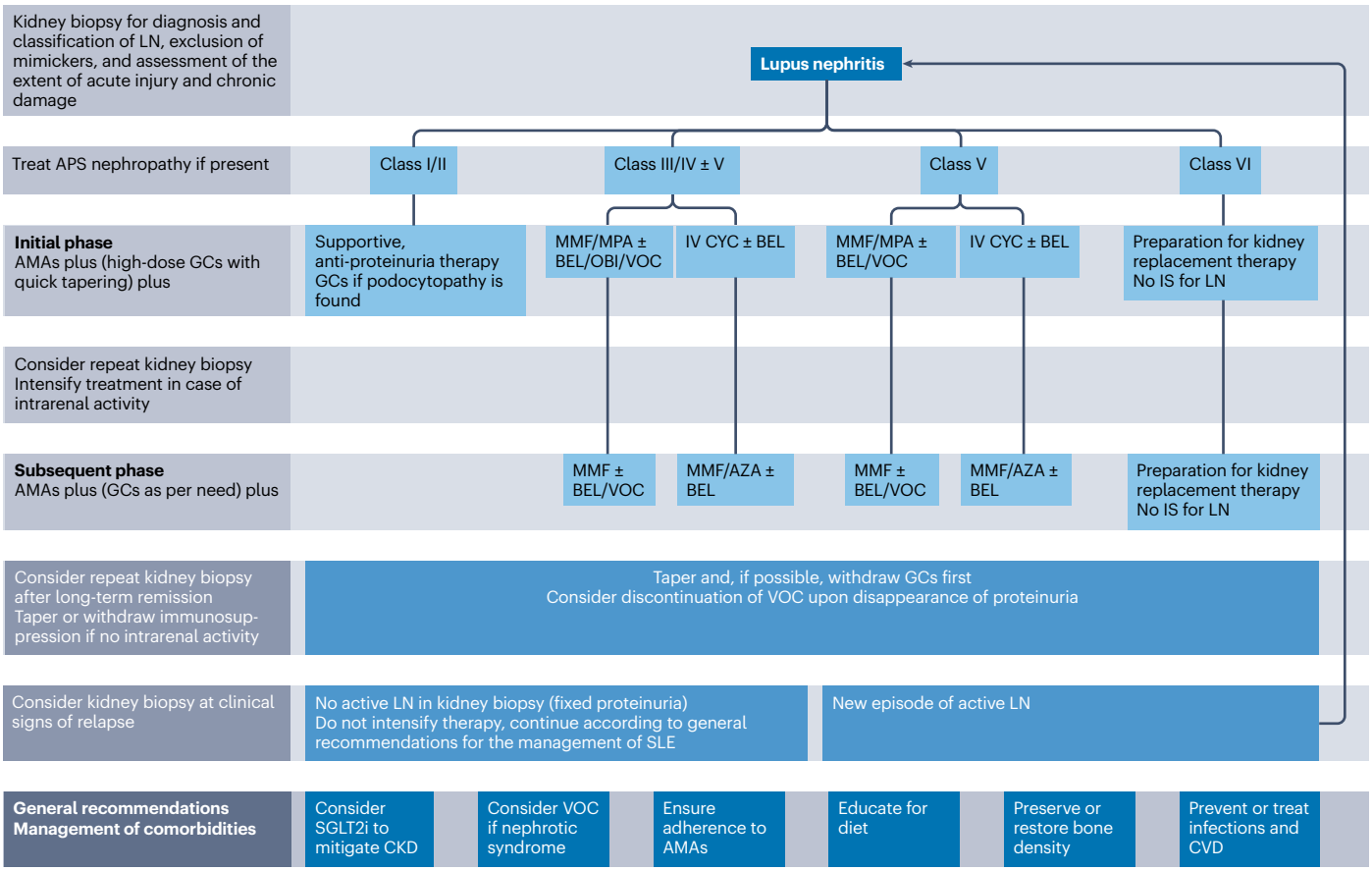

Fig. 5 | Schematic illustration of the management of LN. Lupus nephritis (LN) management is guided by kidney biopsy findings, with treatment tailored to inflammation severity and chronic damage. The primary short-term goal is achieving remission while minimizing treatment-related toxicity, whereas long-term objectives focus on preventing flares, slowing chronic kidney disease (CKD) progression, preserving kidney function, and reducing morbidity and mortality. Immunosuppressive therapy, including glucocorticoids (GCs) and targeted agents, is used to control disease activity. Adjunctive measures, such as blood pressure control and renin–angiotensin–aldosterone system–sodium–glucose co-transporter 2 (RAAS–SGLT2) inhibition, help protect renal function. Findings of new clinical trials resulted in the introduction of multi-agent regimens that improve kidney outcomes. However, treatment remains individualized, considering patient characteristics and biomarkers of response. AMA, antimalarial agent; APS, antiphospholipid syndrome; AZA, azathioprine; BEL, belimumab; CVD, cardiovascular disease; CYC, cyclophosphamide; IS, immunosuppressants; IV, intravenous; MMF, mycophenolate mofetil; MPA, mycophenolic acid; OBI, obinutuzumab; SGLT2i, SGLT2 inhibitor; SLE, systemic lupus erythematosus; VOC, voclosporin.

by the level of histological activity; however, this guidance has not yet been directly examined in trials[7]. Importantly, data regarding treatment for classes I and II are limited. Class VI LN designates advanced chronic kidney damage resulting from any class of previously active LN and implies an impending need of kidney replacement therapy.

For active LN, management aims to prevent further damage accrual and kidney function loss through a dual approach of controlling immunological activity and mitigating the effects of nephron loss due to disease-mediated chronic injury. Prompt diagnosis and early initiation of treatment are critical to minimize chronic kidney damage[156,157]. Systemic glucocorticoids combined with immunosuppressive drugs rapidly control intrarenal inflammation and attenuate autoimmune activity[158]. Blood pressure control, inhibition of the renin–angiotensin–aldosterone system (RAAS) and inhibition of the sodium–glucose co-transporter 2 (SGLT2) slow the progression of CKD caused by nephron loss by reducing the glomerular filtration pressure, hyperfiltration and metabolic workload in the proximal tubules[4–6,101].

Background therapy with antimalarial agents

Antimalarial agents, particularly hydroxychloroquine due to its safety profile, are recommended for all patients with SLE unless contraindicated[159–161]. Among multiple benefits, antimalarial agents reduce the risk of new or recurrent LN and progression to kidney failure, possibly by interfering with the actions of Toll-like receptors[14,162,163]. Routine screening for antimalarial treatment-induced retinopathy is advised, with specific dosing considerations for patients with impaired kidney or liver function due to altered antimalarial drug clearance[164].

Classes I and II LN and lupus podocytopathy

Robust evidence for the management of class I or II LN is lacking. All patients with proteinuria should receive RAAS-blocking agents, maintain good blood pressure control and adhere to a sodium-restricted diet[165]. Routine immunosuppression is not currently recommended.

Lupus podocytopathy may occur alone or with class I or II LN. Histologically, lupus podocytopathy resembles minimal change disease

or focal segmental glomerulosclerosis. For patients with a minimal change pattern, glucocorticoids are often sufficient. Patients with focal segmental glomerulosclerosis morphology may require azathioprine or a calcineurin inhibitor in addition to glucocorticoids[4,5,101].

Class III or IV with or without class V LN

Initial treatment for active disease. In addition to background antimalarial therapy, current guidelines recommend initial therapy with systemic glucocorticoids to attenuate inflammation quickly[4,5]. High-dose glucocorticoids were used historically, but clinical trials in the past 5 years suggest lower doses may be sufficient[166–171].

To control autoimmunity and prevent recurrent LN episodes, one or two immunosuppressive agents are combined with glucocorticoids[172], referred to in the ACR guidelines for the management of LN as dual and triple therapy, respectively[7]. MMF or mycophenolic acid (MMF/MPA)[169–171], or intravenous cyclophosphamide (most commonly low dose as in the Euro-Lupus Nephritis Trial)[167,168] are used in dual therapy regimens[4–6]. Following large randomized controlled trials (RCTs) that reported results between 2019 and 2021, the approvals of the BAFF inhibitor belimumab and the calcineurin inhibitor voclosporin offer the opportunity for multi-agent regimens without increased treatment-related toxic effects. Voclosporin was added to glucocorticoids and MMF[173,174] and belimumab was added to glucocorticoids and either MMF or low-dose cyclophosphamide[175]. Compared with dual therapy plus placebo, significantly more patients receiving a multi-agent regimen with add-on belimumab (43% versus 32%, $P = 0.03$) or voclosporin (43% versus 23%, $P < 0.0001$) achieved complete renal response at 1 or 2 years. In addition, a phase III RCT of the anti-CD20 monoclonal antibody obinutuzumab, released in early 2025, showed a complete renal response at week 76 in 46% of patients in the obinutuzumab group compared with 33% in the placebo group ($P = 0.02$)[176]. These findings are likely to support its approval as part of a multi-agent regimen together with MMF. Of note, the trials of multi-agent regimens maintained patients on the same immunosuppressive drugs from initiation until the end of the study period (2–3 years). Conceptually, this approach blurred the traditional distinction between induction therapy and maintenance therapy, as it was defined in older cyclophosphamide regimens, and instead constitutes a more continuous therapeutic strategy.

Currently, there is little information to guide the choice of initial therapy. Multi-agent regimens might offer better renal remission rates than dual therapy, but cost and access must be considered. Ideally, treatment should be individualized based on patient characteristics and biomarkers of response[177]. Subgroup and post hoc analyses of the voclosporin, belimumab and obinutuzumab LN trials provide information that may help in selecting a suitable multi-agent regimen. Belimumab was most effective when added to MMF and in patients with low proteinuria levels (<3 g/day), prevented LN flare and attenuated a fall in GFR over time[178–182]. Obinutuzumab was most effective in patients with high proteinuria levels (UPCR ≥3 g/g), serological activity (high anti-dsDNA antibody, low C3 or low C4 levels) and in those with concomitant class V LN alongside class III or IV; however, patients with pure class V LN were not included in the trial[176]. Voclosporin was effective with rapid glucocorticoid taper at all levels of proteinuria and, being a calcineurin inhibitor[50], it protects against podocyte loss, a glomerular injury associated with progressive CKD[183,184].

Subsequent treatment. After an arbitrarily defined duration, standard practice has been to decrease the intensity of initial therapy and provide modest long-term immunosuppression[185]. This approach reduces the chances of adverse treatment events and provides time to consolidate treatment response into complete renal response (also arbitrarily defined)[185]. Resolution of LN (both clinically and histologically) takes a long time and often does not occur during initial therapy; thus, primary end points in LN trials are set for 12–24 months from baseline. When a per-protocol repeat kidney biopsy is performed, proposed tissue-based definitions of remission and response may help guide subsequent therapy[186].

Low-dose cyclophosphamide entails treatment for 3 months, followed by a switch to MMF/MPA or azathioprine[4–6,101,187]. Initial therapy with MMF/MPA continues with a reduced dose after the first 6–12 months. If possible, glucocorticoids should be discontinued or maintained at very low levels. The overall duration of immunosuppression for LN has not been definitively determined but is recommended to extend for at least 3 years[4–6,101,187–190].

Subsequent therapy after starting with a multi-agent regimen is unclear. The BLISS-LN trial continued belimumab with a reduced dose of glucocorticoids and MMF for 2.5 years, maintaining efficacy with a low adverse effect profile[181]. Similarly, in the AURORA-2 trial, patients remained on voclosporin for 3 years combined with a reduced dose of MMF[183]. No clear data exist for other agents or beyond these timepoints.

Class V LN

Evidence for immunosuppressive therapy in pure class V LN is limited owing to its low representation in LN trials. Immunosuppressive treatment is typically initiated for persistent proteinuria >1 g/24 h after conservative management with blood pressure control, RAAS inhibition and sodium restriction[4,101]. Regimens do not differ from those described for class III or IV LN with or without class V LN. Calcineurin inhibitors and the B cell-targeting biologic rituximab are often used based on their efficacy in primary membranous nephropathy[191–193]. Treatment intensity for patients with pure class V LN may also be influenced by systemic lupus symptoms.

LN therapy beyond immunomodulation

Patients with LN often face comorbidities from SLE, CKD and immunosuppressive treatments, necessitating active management and appropriate measures (Fig. 6).

Kidney injury response modification. Despite achieving a clinical response, most patients with LN experience considerable nephron loss, even during the first episode of LN[86] (Fig. 4). This chronic damage defines CKD and increases with subsequent episodes of active LN. Patients with LN and CKD are at high risk for cardiovascular morbidity and progression to kidney failure. Hence, injury response modification that slows CKD progression should be considered to complement immunosuppressive therapy[4,5]. Injury response modifiers target mediators of CKD progression, including systemic hypertension, intraglomerular hypertension, single-nephron hyperfiltration and persistent proteinuria. Patients with LN should maintain a healthy weight, limit dietary sodium intake, maintain meticulous blood pressure control and receive treatment with RAAS inhibitors[165]. Despite limited or no evidence in LN specifically, SGLT2 inhibitors and GLP-1 RAs may also be considered for CKD mitigation[4].

Infections. Patients on immunosuppressive therapy need vigilant monitoring for infections[4,5]. In regions with high hepatitis B and tuberculosis prevalence, screening for these diseases is important and vaccination should be considered for patients who will be exposed to potent

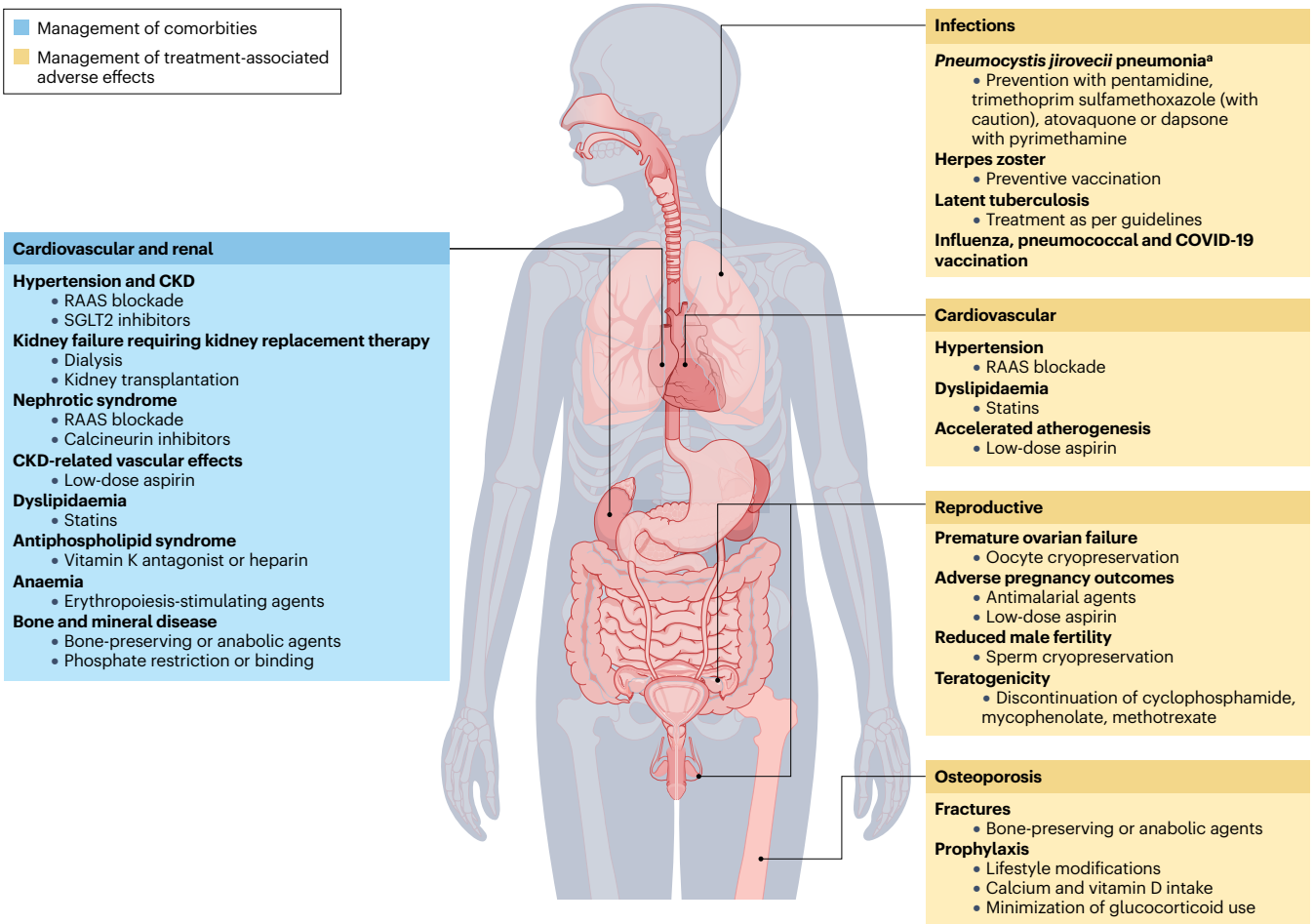

Fig. 6 | Management of comorbidities and treatment-associated adverse events in lupus nephritis. Management of lupus nephritis should involve management of comorbid conditions and treatment-associated adverse events, according to current guidelines[4,5]. Common comorbid conditions include antiphospholipid syndrome, hypertension, dyslipidaemia, chronic kidney disease (CKD)-related complications, anaemia and kidney failure. Treatment-associated adverse events include infections, hypertension, dyslipidaemia, accelerated atherosclerosis, adverse pregnancy outcomes and osteoporosis. [a]Prophylaxis for this infection is indicated for high-risk patients, with caution, according to local guidelines. RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2. Reprinted from ref. 3, Springer Nature Limited.

immunosuppression[4]. Influenza, herpes zoster and pneumococcal vaccines are recommended before starting immunosuppression[4,194]. Live vaccines should be avoided[4,194] because, even though attenuated, the organisms in a live vaccine may proliferate in an immunocompromised host. However, in patients with urgent treatment needs, immunosuppression should not be unnecessarily delayed while awaiting vaccine responses[195].

Cardiovascular disease. In addition to SLE itself, risk factors for accelerated atherogenesis and cardiovascular disease include hypertension, CKD, nephrotic syndrome, prolonged glucocorticoid use, obesity, diabetes mellitus, smoking, hyperlipidaemia and APS. Aggressive management of these conditions is crucial[4,196], but current control of risk factors is inadequate[197], highlighting the need of increased awareness. Hydroxychloroquine and low-dose aspirin use may reduce the cardiovascular disease risk[4,196,198]. Vitamin K antagonists or heparin are indicated for LN with concomitant APS nephropathy[4].

Osteoporosis. Patients with SLE have around twice the risk of developing osteoporosis compared with healthy individuals, and those with LN have an around 1.6-fold higher risk than patients with SLE without LN[199,200]. Fracture risk should be assessed within 6 months of glucocorticoid treatment and every 2–3 years thereafter[201]. Preventive measures include lifestyle modifications, adequate calcium and vitamin D intake, and minimization of glucocorticoid use. Drug options include oral bisphosphonates, teriparatide and denosumab, with caution advised for patients with impaired kidney function[202]. Oestrogen-containing agents are generally not recommended owing to the risk of thrombosis[203].

Fertility and pregnancy in LN

Fertility concerns should be addressed at the start of therapy, especially if patients will be treated with high-dose cyclophosphamide, which has a risk of premature ovarian failure in women and azoospermia in men[4]. Although high-dose cyclophosphamide is now used less frequently

than in the past, ova or sperm cryopreservation should be considered before cyclophosphamide commencement. If cryopreservation is not accessible, ovarian and testicular protection with leuprolide or testosterone, respectively, should be considered[204,205].

Unplanned pregnancies during active LN may exacerbate disease activity, leading to poor fetal and maternal outcomes. Continuing hydroxychloroquine[206] and starting low-dose aspirin[207] is advised for all pregnancies in patients with LN and can help prevent preeclampsia. Preconception counselling, coordination of care among rheumatologists, nephrologists and obstetricians, and effective contraception are important[208,209]. If a patient with LN becomes pregnant and needs treatment, pregnancy-compatible drugs, such as azathioprine, tacrolimus and ciclosporin, may be used[210]. Cyclophosphamide, MMF/MPA, methotrexate and leflunomide should be avoided[210]. Low-molecular-weight heparin is recommended along with low-dose aspirin if APS coexists[211].

Patient education and support

Educating patients about LN, treatment options and the importance of adherence to therapy is crucial. Education programmes should provide comprehensive information on medication adverse effects, lifestyle modifications and strategies to manage flares[212,213]. Living with LN can be challenging, and patients may benefit from psychosocial support. Non-adherence is a particularly challenging issue to detect and manage[212,214]. In addition to direct patient questioning and reviewing pharmacy refill records, adherence can also be assessed by measuring drug levels, such as hydroxychloroquine or MPA concentrations[215–218]. Importantly, non-adherence may be misinterpreted as treatment resistance, potentially leading to inappropriate escalation of therapy, persistent disease activity, and flares. Some investigators have suggested that medication non-adherence is a considerable risk factor for progression to kidney failure[219,220]. Counselling services and support groups can provide emotional support, improve coping strategies and enhance overall quality of life[213].

Quality of life

In patients with SLE, LN worsens health-related quality of life (HRQoL)[221]. The key goal of LN treatment is to improve kidney survival without further compromising HRQoL. Most previous LN studies used generic instruments for assessing HRQoL, such as the Medical Outcomes Study 36-item Short Form health survey (SF-36). A cross-sectional survey reported considerably poorer scores in the physical functioning, role physical, and social functioning domains of SF-36 in patients with active compared with those with inactive LN[222]. A Swiss study demonstrated an association between LN activity and poor scores in the role emotional, role physical and, to a lesser extent, bodily pain, vitality and social functioning domains of SF-36 (ref. 223). Similarly, in a study from Iran, HRQoL experience was worse in patients with SLE who had kidney involvement than in those without[224]. However, reported results have not always been consistent. In an Italian study[225] and a report from the multinational Systemic Lupus International Collaborating Clinics inception cohort of SLE patients[14], LN was, in general, not associated with worse HRQoL than SLE without LN. However, the subgroup of patients with eGFR levels <30 ml/min reported considerably reduced scores in the physical functioning, role physical and bodily pain domains of SF-36 (ref. 14). Finally, in Chinese patients with SLE, musculoskeletal but not renal flares in the preceding year were associated with worse physical and mental health scores in SF-36 (ref. 226).

The discrepancies in the relationship between LN and worse HRQoL may be explained by several factors, including differences in sample size, the proportion of patients with active LN, varying stages of CKD, varying severity of LN, concomitant use of glucocorticoids and immunosuppressive therapies, as well as the tools used to assess HRQoL. Nevertheless, patients with LN and severely impaired kidney function have consistently reported poorer HRQoL in the physical component summary and the general health domain of SF-36 (refs. 14,227). Although impairments of HRQoL in patients with kidney failure are not specific to LN, kidney replacement therapy has been shown to improve HRQoL regardless of the aetiology of underlying CKD[228].

Using the LupusPRO, a validated SLE-specific patient-reported outcome (PRO) measure, a multinational study comparing patients with SLE and active LN with those without active LN reported poorer scores both in health-related and non-health-related (desire/goal, social support, coping and satisfaction with medical care) quality of life, especially in the lupus medication and procreation domains[229]. Being SLE-specific, LupusPRO captures the unique aspects of living with SLE, including the effects of lupus symptoms alongside emotional wellbeing and relationships. Another SLE-specific PRO measure, the LupusQoL, has also been shown to be sensitive to change with the health status reported by patients[230], and its content validity in LN has been supported by qualitative interviews[231]. However, further validation in LN studies is needed.

The presence of non-renal disease activity in patients with LN has also been shown to contribute to poor HRQoL in the domains of pain, ability to participate in social roles, physical function and fatigue[232]. Symptoms such as fatigue, fibromyalgia, mood disturbances and brain fog, each contributing substantially to reduced quality of life, have been shown to pose a similar burden in patients with active renal and non-renal SLE, and may ameliorate as nephritis improves[233].

Some insights come from past prospective LN trials that included HRQoL as a secondary end point[234,235], but not all LN RCTs have incorporated HRQoL measures[174,175]. The importance of assessing HRQoL cannot be overemphasized, and incorporating PROs in major LN trials should become standard practice in the future.

Outlook

Clinical parameters and biomarkers

As a severe manifestation of SLE, LN requires a strategic and multifaceted approach to ensure optimized patient outcomes[3]. Despite an improved understanding of LN pathogenesis and the advent of promising new therapies, several questions are yet to be addressed. How to clinically distinguish immunological SLE activity from non-immune causes of persistent proteinuria remains unsolved. Predicting and monitoring response to treatment is complicated owing to discordance between clinical parameters and histological findings, frequently necessitating a repeat kidney biopsy to guide and personalize management[106,111,137]. Individualized management will be facilitated as the focus of the kidney biopsy shifts beyond histological descriptions to incorporate molecular characterization of the kidney tissue, including not only the glomerular but also the tubulointerstitial compartment[106].

Various histological, serological and urinary parameters have been evaluated as biomarkers for SLE and LN in the past three decades, including chemokines, cytokines, growth factors, pro-inflammatory factors, adhesion molecules and cell markers, but few have been validated and data from longitudinal LN cohorts are scarce[131,236]. As a result, predicting disease evolution, LN flares and progression to kidney failure requiring kidney replacement therapy is still a clinical challenge. In this context, several markers might be promising, including urinary $CD4^+$ T cell counts for detecting and monitoring proliferative LN[237],

Box 4 | Next steps to improve patient outcomes

- Move beyond invasive biopsies by rigorously testing promising urine-based markers in longitudinal patient cohorts.
- Integrate molecular profiling (spatial transcriptomics and proteomics) into baseline and follow-up kidney biopsies to identify distinct lupus nephritis subtypes and molecular pathways, and to guide personalized therapy.
- Redesign clinical trials with more sensitive renal end points and refined patient selection (for example, by making use of the type I interferon signature).
- Establish standardized protocols for B cell-depleting therapies defining optimal antigen targets, dosing schedules, response biomarkers and toxicity management strategies.
- Define clear criteria for assessment, flare and tapering biopsies to optimize timing and minimize unnecessary procedures.
- Incorporate patient-reported outcomes (for example, LupusPRO) as routine secondary end points, with culturally adapted digital tools for real-time quality-of-life monitoring.
- Strengthen multidisciplinary care pathways by integrating rheumatology, nephrology, nutrition and mental health support.
- Collaborate with payers and health systems to ensure equitable access to advanced biologics and biosimilars, backed by robust cost-effectiveness data.

a composite biomarker of urine CCL2 and serum creatinine shown to relate to tubulointerstitial inflammation[238], and urine IL-16 and CD163 shown to mirror intrarenal LN activity[239–241]. In addition, the potential utility of urine-activated leukocyte cell adhesion molecule (ALCAM) was shown to be a versatile marker of LN in multiple cohorts[242,243], also pointing to the CD6–ALCAM pathway as a potential therapeutic target[244]. This field of investigation is likely to mature in the coming years, and multiple efforts are underway to test lead biomarker candidates across multiple cohorts and to undertake comprehensive spatial omics screens of LN kidneys.

Current trials and new potential targets

New glucocorticoid-sparing biologics and small-molecule inhibitors that can replace the nonspecific immunosuppressants in current use are very much needed. Many new developments raise hope in this area. More effective combinatorial use of currently approved drugs has been recommended by EULAR, ACR and Kidney Disease: Improving Global Outcomes in the past 2 years[4–7]. Belimumab, obinutuzumab or calcineurin inhibitors can be added to standard therapy with glucocorticoids and MMF/MPA or intravenous cyclophosphamide to increase the chance of achieving a complete kidney response, avoid flares and decrease glucocorticoid doses[4–6]. A phase III LN RCT evaluated the anti-CD20 monoclonal antibody obinutuzumab, which induces deep B cell depletion[245], as an add-on to MMF and achieved its primary and key secondary end points in early 2025 (ref. 176). Early case series of anti-CD19 CAR T cell therapy in refractory LN report remarkable clinical and immunological responses, including sustained remission in patients unresponsive to other B cell-depleting drugs[246–250]. Ongoing efforts aim to define optimal targets (for example, CD19 and long-lived plasma cell antigens), dosing and safety profiles before wider clinical adoption. Furthermore, plasma cell depletion with anti-CD38 monoclonal antibodies showed efficacy in refractory LN[82] and is being trialled in early phase programmes. Immunoablative therapy with autologous stem cell transplantation induced 5-year disease-free survival in >50% of patients with refractory LN, albeit with a 27% relapse rate and a high degree of morbidity[251].

Targeting the IFN-I pathway may also hold promise; antagonising the type I interferon receptor with anifrolumab has resulted in its approval for extra-renal SLE and is being evaluated in LN[252] (Supplementary Table 1). These developments should be coupled with systematic efforts to improve biomarker validation, clinical trial design, multidisciplinary care and equitable treatment access to truly transform outcomes in LN (Box 4). Eventually, the availability of biosimilars and generic compounds may expand drug access to a larger patient population.

Lifestyle interventions

The primary goal of LN treatment is to reduce the risk of kidney failure, morbid and comorbid burden, and mortality, without compromising patients' quality of life[3]. Current tools for assessing HRQoL in LN require refinement. Patient education on adherence to medications and a healthy lifestyle (including a balanced diet, salt reduction, regular exercise, weight control, smoking cessation and alcohol restriction), as well as psychosocial support, are important in the management of SLE and LN[213].

Conclusions

Along with appropriate pharmacotherapy, multidisciplinary care tailored to the patient's individual needs, involving rheumatologists, nephrologists, social workers and other health professionals, is crucial for holistically addressing both the immune and non-immune risk factors for progressive kidney function loss and for maximizing kidney lifespan in LN. Despite these challenges, the compelling advancements in basic research, diagnostics, treatments and monitoring strategies for LN raise hope and promise for the future.

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This seminal work introduces a pathophysiology-driven framework for diagnosing and managing LN, offering mechanistic insights that inform current and emerging therapeutic strategies.

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All authors contributed to all sections of the Primer. Oversight of the Primer (C.M.).

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