A pathophysiology-based approach to the diagnosis and treatment of lupus nephritis

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Hans-Joachim Anders[1] and Brad Rovin[2]

[1]Medizinische Klinik and Poliklinik IV, Klinikum der Universität München, Munich, Germany; and [2]Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Lupus is no longer an unknown chameleon of medicine. Significant progress has been made on unraveling the pathogenesis of lupus and lupus nephritis, and how to treat the disease. Here we provide an update on the pathophysiology of lupus and its related kidney disease, consider areas of controversy in disease management, and discuss the unmet needs of lupus nephritis and how to address these needs. We focus on rethinking how innovative therapies for lupus nephritis should be evaluated and evolving strategies to more efficiently mitigate irreversible nephron loss in patients with lupus nephritis.

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Correspondence: *Hans-Joachim Anders, Medizinische Klinik and Poliklinik IV, Klinikum der Universität München – Innenstadt, Ziemssenstr. 1, 80336 Muenchen, Germany. E-mail: hjanders@med.uni-muenchen.de; and Brad Rovin, Ohio State University Wexner Medical Center, Division of Nephrology, 395 W 12th Ave, Columbus, Ohio 43210, USA. E-mail: rovin.1@osu.edu*

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The diagnosis of lupus nephritis (LN) implies significant morbidity and mortality, especially if LN cannot be controlled and ongoing loss of nephrons occurs. This is illustrated by a recent outcomes analysis of an inception cohort of 1827 new systemic lupus erythematosus (SLE) patients followed up from 1999 to 2012.[1] The cohort was 89% women, of which were 49% white, 17% black, 15% Asian, and 15% Hispanic. The overall incidence of LN in this population was 38%. After adjusting for sex, enrollment age, and race/ethnicity, the hazard ratio for death (vs. no LN) was 3.2-fold, and the 10-year cumulative incidence of end-stage renal disease (ESRD) and death among the LN patients was 10.1% and 5.9%, respectively. Although significant progress has been made in understanding the pathogenesis of SLE, management of LN remains unsatisfactory. In this review we focus on recent advances in the pathophysiology of LN and how to further improve LN management and outcomes using these advances.

Central avenues in the pathophysiology of SLE and SLE-related kidney diseases

Autovaccination against nuclear antigens. The central paradigm of SLE is the loss of immune tolerance to nuclear autoantigens, based on bypassing checkpoint mechanisms that normally assure self-tolerance.[2] Checkpoint mechanisms include, for example, avoidance of nuclear material exposure to immune recognition receptors via strict compartmentalization to the intracellular space, apoptotic rather than necrotic cell death, rapid phagocytosis of dead cells, and masking of any potential autoadjuvant activity of self-nucleic acids, for example by the methylation of immunostimulatory RNA and DNA sequences.[3] The genetic heterogeneity of the global population implies that everyone maintains immune tolerance a bit differently,[4] which is also supported by a variable prevalence of SLE in different populations. Patients with SLE carry an unfortunate combination of genetic variants that compromises immune tolerance to nuclear material at many of the aforementioned checkpoints, often at the same time. Importantly, each patient has his or her own combination of genetic susceptibilities, and therefore SLE is usually not monogenic but is a polygenic disorder inherited as a Mendelian trait.[4] Familial SLE or sporadic monogenic SLE does occur but is rare and only seen when a single (mutation-like) gene variant elicits a very prominent effect on tolerance, such as complement C4 or TREX1 deficiency.[5,6] Therefore, SLE is a clinically defined syndrome with several causes rather

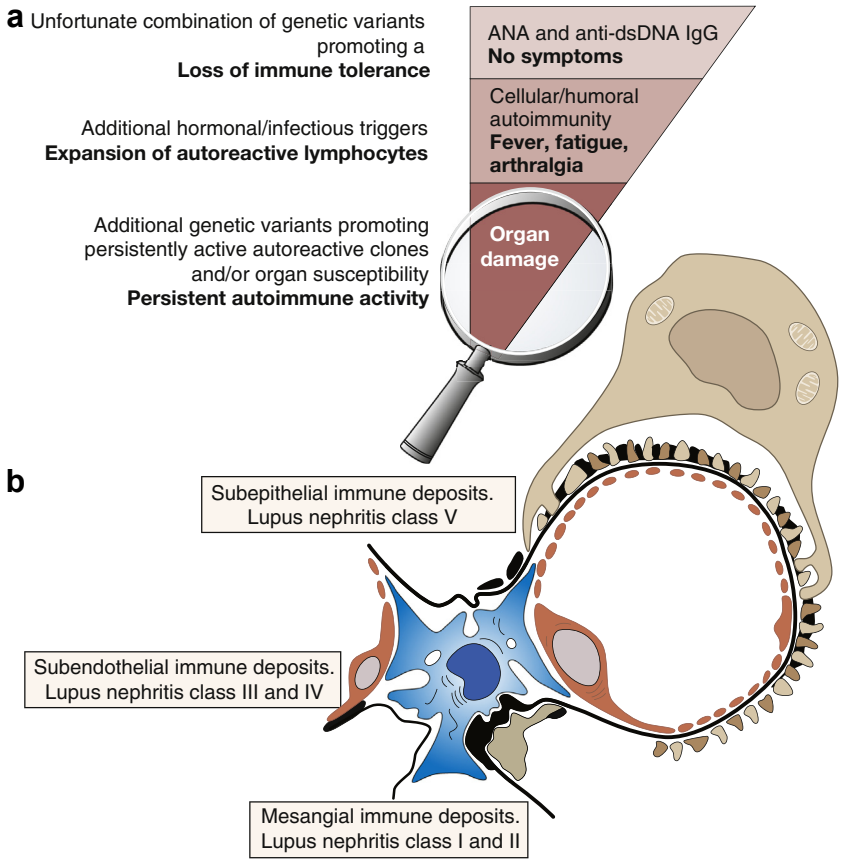


Figure 1 | Pathogenesis of lupus nephritis. Lupus nephritis develops in individuals with an unfortunate combination of genetic variants that compromise the maintenance of immune tolerance to endogenous nuclear material (**a**). The consequence of tolerance loss is autovaccination and lifelong persistence of antinuclear antibodies (ANA), indicating persistently active autoreactive T- and B-cell clones. Only a subset of patients develops clinical symptoms, often upon (viral) infections or hormonal influences that provide an unspecific stimulus for the expansion of these autoreactive lymphocyte clones. The symptoms depend on interferon-alpha release, hence they are unspecific just as in any viral infection. A further subset of patients develops organ manifestations such as lupus nephritis, which depends on the presence of additional susceptibility genes, some of which affect the kidney itself, whereas others drive persistent systemic inflammation and autoimmunity. The inverted triangle indicates the prevalence of the respective stage of the syndrome. Inside the kidney, lupus nephritis is an immune complex glomerulonephritis (**b**). Other types of renal injury may occur in patients with lupus either alone or with lupus nephritis, including thrombotic microangiopathy and renal vasculitis (not shown). Immune complexes can deposit in the subendothelial, mesangial, or subepithelial compartments of the glomerulus. The location of immune complex accumulation defines the different histopathological classes of lupus nephritis according to the current International Society of Nephrology/Renal Pathology Society classification. Because these classes differ in terms of prognosis and management, a kidney biopsy is usually required. dsDNA, double-stranded DNA.

than a disease with a single cause.[7] Hormonal or X-chromosomal factors certainly play an important role as the male-female ratio of SLE is 1:9. A unifying pathway present in every SLE patient is the overt autovaccination/immunization to nuclear material exemplified by the presence of antinuclear antibodies.[7] This implies, potentially, that lifelong immune memory is established in the memory T cells of lymphoid organs and in long-lived plasma cells in the bone marrow.[8] The concept of autovaccination is useful because patients can understand that after autovaccination has occurred their immune systems will remain primed like after other vaccine shots, and so there is no cure for SLE but lifelong monitoring and suppression of autoimmune disease activity are necessary.[8] The diagnostic hallmark of circulating antinuclear antibodies consists of various specificities depending on the dominant antigens during the autovaccination process.[7] This humoral autoimmunity is accompanied by less clinically evident expansion of autoreactive T cells and T cell–mediated autoimmunity. Epitope spreading can cause additional autoimmune manifestations such as secondary Sjogren's syndrome or antiphospholipid antibody syndrome in patients with lupus.[9]

Lupus autoantigens trigger immune responses and symptoms similar to viral infection. Loss of immune tolerance and antinuclear antibodies production does not necessarily produce any clinical symptoms (Figure 1a). Often, however, immune recognition of endogenous nucleic acids via Toll-like receptors 7 and 9 induces interferon-α–dependent antiviral immunity, which manifests clinically as fatigue, fever, arthralgia, and myalgia, as may be seen in any viral infection.[10–12] This central role of antiviral immunity in the pathogenesis of SLE has been referred to as "pseudoantiviral immunity."[13] SLE activity can be influenced by environmental factors that contribute to DNA unmasking (certain drugs)

and massive cell death (ultraviolet light), or that provide an unspecific immunostimulatory effect to autoreactive lymphocyte clones (infections).[7]

Genetic factors determine if and how lupus affects the kidney. A recent meta-analysis of genome-wide association studies revealed that the risk of an SLE patient developing LN depends on additional genetic variants that create a predisposition for significant renal damage during the systemic autoimmune state of SLE.[14] Some gene variants may promote mesangial cell proliferation; others affect basement membrane stability (COLA41) or the multifaceted functions of integrin-alpha M (Mac-1/complement receptor-3, CD11b). Such additional "weaknesses" or susceptibility factors determine whether a patient develops signs of nephritis, that is, hematuria and proteinuria. Immune complex glomerulonephritis in SLE can present in different ways depending on the primary site of immune complex deposition (Figure 1b).[15] It was previously thought that circulating IC deposit passively in the glomerular sieve, but rather IC form *in situ* via the recognition of intrarenal lupus autoantigens in the mesangium, subendothelial space, or outside the glomerular basement membrane between podocyte foot processes. Once formed, immune complexes activate complement, which can injure adjacent cells, leading to either mesangial LN (International Society of Nephrology/Renal Pathology Society class I, II), endothelial-proliferative LN (class III, IV), nephrotic syndrome (class V), or various combinations of these.[15] The precise location of IC formation inside the glomerulus determines the type of glomerular cell that is preferentially activated and injured, for example, the mesangial cell in class II (low risk of chronic kidney disease [CKD] and ESRD), the glomerular endothelial cell in class III/IV (high risk of CKD and ESRD), or the podocyte in class V and VI (high risk of CKD and ESRD) (Figure 1). Necrotizing and crescentic glomerulonephritis are less common lesions of this process. Secondary podocytopathy causing podocyte loss and progression from focal-segmental to focal-global glomerulosclerosis is the pathomechanism that turns class III/IV into VI and underlies a progressive decline of glomerular filtration rate (GFR) to ESRD. LN patients of African ancestry show a high prevalence of APOL1 gene risk alleles, which implies a risk for faster CKD progression and ESRD.[16] IC accumulation also occurs in peritubular capillaries, causing interstitial inflammation and, in advanced disease, tertiary lymphoid organ formation in the renal interstitium.[17] Isolated tubulointerstitial nephritis with predominant B and plasma cell infiltrates, as seen in primary Sjögren's syndrome, is less common. Intrarenal inflammation is maintained via local cytokine and chemokine production, which attracts leukocytes into the glomerulus and interstitium, which further amplify local inflammation, renal cell loss, and nephron atrophy.[18,19] This process is associated with extensive intrarenal microRNA expression and subsequent excretion in the urine, but the functional contributions of these microRNAs to the progression of lupus nephritis *in vivo* has not yet been well characterized. Although GFR is not always impaired during the first episode of LN, subsequent flares often show decreased renal excretory function as a late marker of underlying progressive nephron loss (Figure 2). On renal biopsy, nephron loss presents as glomerulosclerosis as well as interstitial fibrosis and tubular atrophy, referred to as chronic lesions downstream of the injury process.[20]

Kidney disease in SLE other than immune complex glomerulonephritis. Kidney disease in SLE may not always be IC-mediated LN.[21] Thrombotic microangiopathy is far more frequently found in kidney biopsies of lupus patients than previously reported.[22] It may occur as a complication of SLE-related secondary antiphospholipid antibody syndrome or independent from the presence of antiphospholipid antibodies.[22] CKD in older SLE patients without previous episodes of LN may be a consequence of underlying nephron loss due to the nephropathy of aging (Figure 2). Of considerable concern in patients who have had SLE for a long time and have been treated with corticosteroids for many years is the

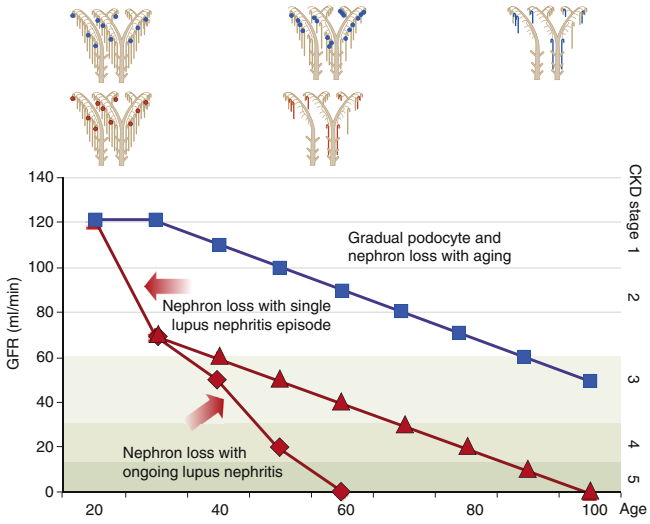
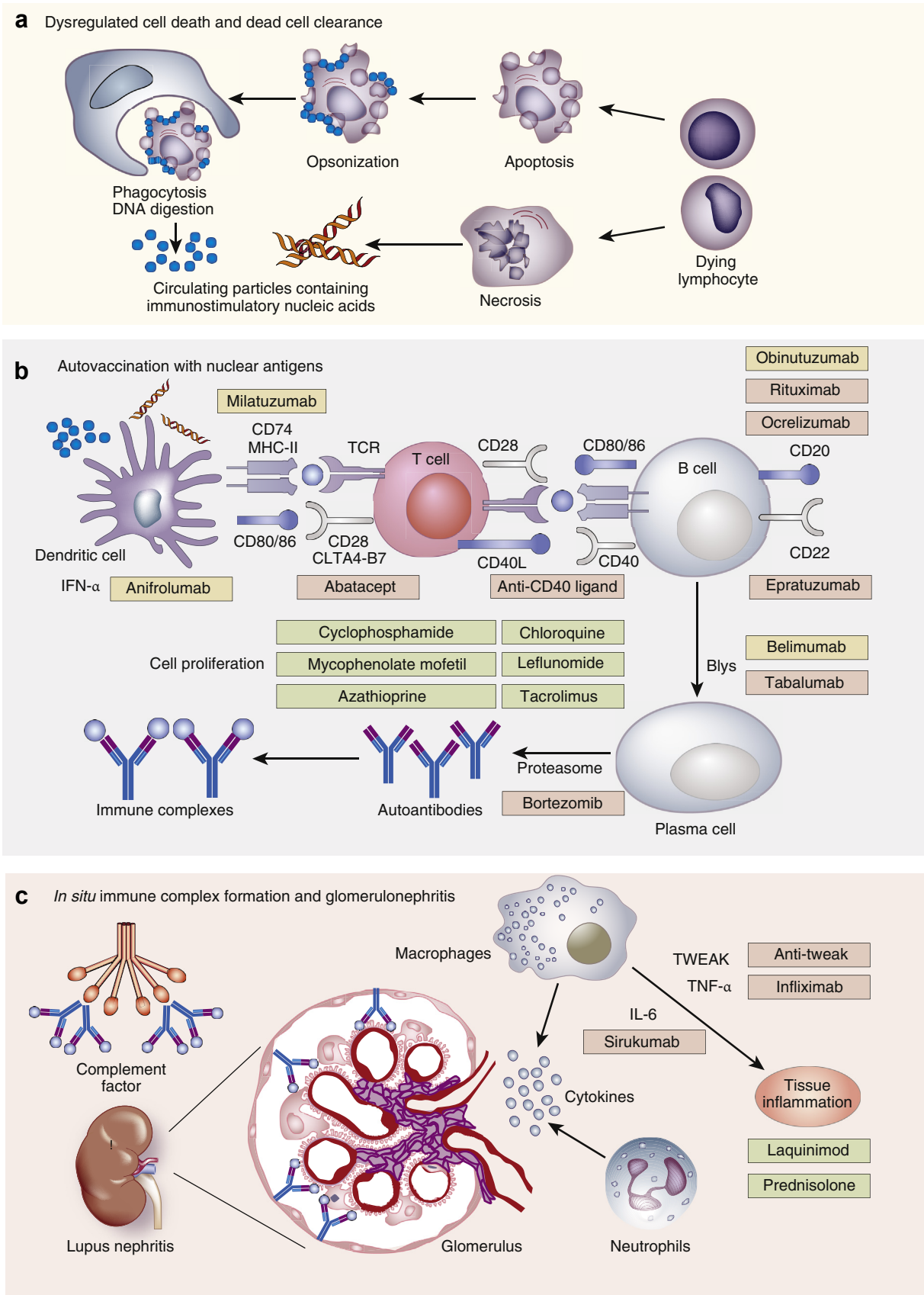


Figure 2 | Preventing nephron loss to improve long-term outcomes of lupus nephritis. Adults continuously lose podocytes that are not replaced. This first leads to focal-segmental and later to focal-global glomerulosclerosis. This is a cause for aging-related nephron loss and the increased incidence of chronic kidney disease (CKD) in the elderly population. A single episode of lupus nephritis early in life, even if well treated and controlled, can lead to a significant loss of podocytes and nephrons, which synergizes with aging-related nephron loss later in life. Thus, a history of lupus nephritis is a major risk factor for end-stage renal disease and exaggerated cardiovascular mortality decades before the end of normal life span. Uncontrolled lupus nephritis activity accelerates nephron loss and potentiates the risk for early end-stage renal disease and death. It is of note that glomerular filtration rate (GFR) significantly overestimates nephron number, because the remaining nephrons undergo hypertrophy. This implies that a mildly increased serum creatinine of 1.3 mg/dl representing a GFR of 45 ml/min may be generated by only 35% of the original nephrons, that is, a more advanced loss of kidney mass caused by systemic autoimmunity. This phenomenon goes along with a loss of renal reserve and persistent hyperfiltration, that is, loss of autoregulation of kidney perfusion, which is of particular importance in patients with hypertension. A clinically applicable biomarker of nephron number remains to be identified and validated. Currently used biomarkers such as proteinuria, urinary cells, or urinary sediment do not mirror nephron number. The time scale may be too optimistic for many patients.


a
Dysregulated cell death and dead cell clearance
Phagocytosis
DNA digestion
Opsonization
Apoptosis
Dying
lymphocyte
Circulating particles containing
immunostimulatory nucleic acids
Necrosis
b
Autovaccination with nuclear antigens
Milatuzumab
CD74
MHC-II
TCR
T cell
CD28
CD80/86
B cell
CD20
Obinutuzumab
Rituximab
Ocrelizumab
Dendritic cell
CD80/86
CD28
CLTA4-B7
CD40L
CD40
CD22
IFN-α
Anifrolumab
Abatacept
Anti-CD40 ligand
Epratuzumab
Cyclophosphamide
Chloroquine
Cell proliferation
Mycophenolate mofetil
Leflunomide
Azathioprine
Tacrolimus
Blys
Belimumab
Tabalumab
Proteasome
Bortezomib
Immune complexes
Autoantibodies
Plasma cell
c
In situ immune complex formation and glomerulonephritis
Macrophages
TWEAK
Anti-tweak
TNF-α
Infliximab
IL-6
Sirukumab
Complement
factor
Cytokines
Tissue
inflammation
Laquinimod
Prednisolone
Lupus nephritis
Glomerulus
Neutrophils

development of treatment-induced diseases that can impact the kidney. For example, this can occur in the setting of steroid-induced diabetes or atherosclerosis, leading to diabetic nephropathy or renovascular disease, respectively. Drug toxicity is a general concern, especially in patients with SLE-related arthritis who are often given nonsteroidal anti-inflammatory drugs.[21] Recently, we identified an SLE patient with "refractory" class V LN whose persistent proteinuria and rapid progression to ESRD was driven by a homozygous nephrin mutation.[23] This implies that not only (repeat) kidney biopsies but eventually genetic testing may be needed to unravel the cause of kidney disease in individual SLE patients.[24]

Assessing disease activity of lupus nephritis

A critical factor for the successful management of LN is being able to differentiate active nephritis from chronic kidney damage.[25] This distinction will guide treatment for LN. Presently, disease activity and damage in response to treatment are assessed by measuring renal function and proteinuria. Kidney histology is generally only examined at LN diagnosis or flare, and it is assumed that changes in proteinuria and renal function reflect disease activity within the kidneys. This assumption has been challenged by assessing renal histology during LN treatment.

Repeat kidney biopsies. Protocol repeat kidney biopsy data provide a unique look at how the kidney responds to LN treatment and, more importantly, how well histologic response is reflected by serum creatinine concentration (SCr) or estimated GFR and proteinuria.[25] Biopsies done before and during treatment have shown histologic and clinical findings to be discordant. Six-month biopsies, done after completing induction therapy for proliferative LN, showed that about half the patients still had active renal lesions despite having achieved a complete clinical remission (SCr stable or improved, proteinuria < 500 mg/d).[26] Conversely, at the 6-month biopsy 19% of patients had achieved a complete histologic remission with no evidence of LN activity, but most (62%) of these patients still had proteinuria well over 500 mg/d. Similarly, in a Swedish cohort ($n = 57$) a protocol biopsy about 8 months after the start of induction therapy showed persistent inflammatory activity in 19.5% of complete clinical responders and persistent clinical findings in 41% of patients with complete histologic remission.[27] After 3.5 years of treatment, 18.8% of complete clinical responders still had an National Institutes of Health activity index > 2 on repeat biopsy, and 42% of complete histologic responders still had persistent proteinuria.[28] Persistent histologic activity in the absence of clinical signs after long-term immunosuppression is concerning, adding uncertainty to the management of maintenance immunosuppressive therapy. Similarly, patients with persistent proteinuria after treatment may no longer have histologic activity, but the presence of proteinuria may discourage tapering maintenance therapy. These findings suggest that repeat biopsies combined with clinical data may be helpful in making treatment decisions. Alternatively, clinical measures or biomarkers that more accurately reflect what is occurring in the kidneys are needed.

Novel biomarkers to assess kidney histology. Because clinical measures of kidney function and proteinuria are not sufficiently robust biomarkers of histologic activity, novel biomarkers of disease activity, response to therapy, and long-term outcomes have been sought. Although no putative LN biomarker has been independently validated, several interesting candidates have been identified. For example, urine white blood cell subsets from 19 patients with active proliferative LN were compared with inactive LN or SLE patients with no LN (SLE controls, $n = 79$).[29] Not surprisingly, patients with active LN (based on biopsy in 74% of patients) had significantly more urine macrophages, T cells, and B cells than controls. Receiver operating characteristic analysis was done to determine if any subtype of urine leukocyte could differentiate active from inactive LN. Urine CD8+ and CD4+ T cells had areas under the receiver operating characteristic curve of 1.0 (sensitivity and specificity 100%) and 0.998 (sensitivity and specificity 98%), respectively, suggesting outstanding diagnostic discrimination. Urine T cells were also diagnostically superior to proteinuria (area under the curve $= 0.92$, sensitivity $= 94\%$, specificity $= 84\%$) and SCr (area under the curve $= 0.60$, sensitivity $= 47\%$, specificity $= 79\%$).

Several urine proteins have been proposed as biomarkers of LN.[30] To develop a noninvasive measure of renal histologic activity, 16 putative LN biomarkers described in the literature, plus the traditional clinical biomarkers of complement levels, proteinuria, and eGFR were tested to identify a diagnostic panel that could differentiate between pediatric patients with an NIH activity index > 10 and ≤ 10.[31] Urine for biomarker

Figure 3 | Standard and pipeline drug interventions for lupus nephritis. The cellular and molecular pathophysiologic pathways involved in lupus nephritis and their related therapeutic targets are illustrated in three sections. The persistence of nuclear material and the process of autovaccination cannot yet be targeted with drugs because this precedes the onset of clinical manifestations (**a**). However, preventative measures, such as ultraviolet light protection, can help to avoid a sudden release of nuclear material from dying cells as a trigger of systemic lupus erythematosus flare. The process of autoantigen presentation and activation of autoreactive leukocytes in lymphoid organs can be suppressed or controlled by numerous drugs that nonspecifically (current standard-of-care drugs) or specifically (novel drugs undergoing clinical trials) interfere with this process (**b**). For example, B-cell–targeted therapies ablate an important contingent of the antigen-presenting cells. Tissue injury involves immune complex disease, T-cell–mediated immunity as well as numerous elements of innate immunity such as complement, Fc receptor signaling, cytokines, and chemokines at the peripheral tissue level (**c**). Unspecific immunosuppressive drugs dampen this aspect, but more specific anti-inflammatory drugs are expected to be more potent in controlling tissue inflammation and tissue remodeling. Drugs proven in randomized controlled trials to efficiently control lupus nephritis are shown in green. Drugs that failed in at least one large randomized controlled trial are shown in red. Drugs for which randomized controlled trials are ongoing are shown in yellow. IFN-α, interferon alpha.

Table 1 | Treatment goals in lupus nephritis

Treatment target by priority	Recommended intervention
1. Lupus nephritis-related mortality	Chloroquine or hydroxychloroquine
	Control of blood pressure and hyperlipidemia
2. SLE and LN activity to avoid ESRD	Immunosuppression no less and no more than necessary
3. Hyperfiltration and proteinuria to avoid ESRD	Renin-angiotensin-aldosterone system inhibition
4. Avoid drug toxicity	Infections: Reduce or eliminate corticosteroids, PJP prophylaxis, vaccination, rigorous infection control
	Gonadal function: Reduce or eliminate cyclophosphamide, prophylaxis with GHRH analogs, sperm and egg banking
	Malignancy: Avoid lifetime cumulative cyclophosphamide of over 30 grams
	Fractures: Reduce or eliminate corticosteroids, vitamin D supplementation, osteomimetic drugs, bone density monitoring
	Birth defects: Use rigorous contraception during therapy with mycophenolate mofetil, renin-angiotensin aldosterone inhibition, vitamin K antagonistic oral anticoagulants
5. Symptoms	Nephrotic syndrome: loop of Henle diuretics

ESRD, end-stage renal disease; GHRH, growth hormone–releasing hormone; LN, lupus nephritis; PJP, pneumocystis jeroveccii pneumonia; SLE, systemic lupus erythematosus.

analysis was obtained at the time of diagnostic kidney biopsy. Using stepwise logistic modeling, the optimal panel included 6 novel biomarkers like MCP-1, KIM-1, and NGAL, but no clinical variables. The diagnostic metrics of this panel are excellent, with an area under the curve of 0.92, sensitivity of 90%, specificity of 86%, positive likelihood ratio of 6.3, and a false-positive rate of 14%. This biomarker panel needs to be tested in independent LN cohorts, including adults, before it can be applied clinically. A potential criticism concerns the cut-off level of 10 for activity index. This may not be as useful as being able to detect lower levels of renal activity, because it has been shown that a persistent histologic activity index > 2 after induction therapy portends a poor overall prognosis for long-term kidney function.[32]

Pathophysiology-based management of lupus nephritis

The current landscape of LN treatment and response. Treating a patient requires first to set treatment goals (Table 1). The standard-of-care approach to LN induction therapy for proliferative disease is aggressive immunosuppression with either cyclophosphamide or mycophenolate mofetil combined with the potent anti-inflammatory activity of high-dose corticosteroids.[33] Induction lasts from 3 to 6 months and is followed by a prolonged maintenance phase with mycophenolate mofetil or azathioprine and lower doses of corticosteroids.[33] The duration of maintenance is not clear, and there are few prospective data to guide duration, but this phase generally lasts at least a year and often much longer.[33] In clinical trials, response to therapy is mainly adjudicated in the short term, often 6 to 12 months after starting treatment, although the goal of treatment is long-term preservation of kidney function. Renal response is based on clinical criteria that include proteinuria, SCr or estimated GFR, and the urinalysis or urine red blood cells, and proteinuria is the most significant component of all current response criteria.[34,35] There is no consensus on what the levels of proteinuria, serum creatinine, and hematuria should be. Modest differences in remission criteria may significantly affect clinical trial outcomes.[35,36] Additionally, renal remission criteria have not been studied prospectively to prove they predict long-term kidney outcomes.

To address the question of short-term response criteria and long-term kidney function, *post hoc* analyses of the Euro-Lupus Nephritis and MAINTAIN trials were done to determine whether SCr, proteinuria, or hematuria within the first year of treatment predicted an SCr < 1 mg/dl after 7 or more years of follow-up.[37,38] The Euro-Lupus Nephritis trial compared low-dose with high-dose cyclophosphamide for induction treatment of LN,[39] and MAINTAIN compared azathioprine with mycophenolate mofetil as maintenance therapy.[38] A proteinuria level < 0.7–0.8 g/d at 12 months was the best short-term endpoint for a long-term SCr < 1 mg/dl, with positive and negative predictive values of 88% to 94% and 31% to 67%, respectively. Predictive value was not improved by adding SCr or urine red blood cells to proteinuria at 12 months. Although these results suggest that if proteinuria falls below 0.7 to 0.8 g/d after 12 months of therapy patients have a high likelihood of maintaining good long-term kidney function, this cannot be recommended as the only endpoint for future LN trials because its negative predictive value is poor, and many patients with higher 12-month proteinuria levels did well long term. Additionally, the Euro-Lupus Nephritis and MAINTAIN trials enrolled mainly Caucasian LN patients, and these results may not apply to all populations. Nonetheless, the data suggest that the urine sediment may not need to be a component of renal response criteria for multicenter clinical trials, probably because urinalyses are difficult to standardize across centers.

Despite the aggressive nature of standard-of-care treatment, only 15% to 40% of patients achieve a complete renal response after 1 year.[40] The overall ESRD rate due to LN is about 5 cases/million in the USA, but it is much higher in Hispanics and African Americans.[40,41] The presence of APOL1 risk alleles is a predictor of poor renal outcome in African Americans, but the underlying pathomechanisms are still unknown, and currently there are no specific recommendations for APOL1 variant patients that affect treatment.[16] According to the 2014 United State Renal Data System, ESRD attributable to LN accounts for about 2% of prevalent patients receiving renal replacement therapy. Additionally, induction and maintenance therapy are associated with considerable morbidity.[42] Thus, there has been a

significant effort to develop LN therapies that are more effective and less toxic. The basis for these novel therapies is our advanced understanding of the pathophysiology of LN.

Matching pathogenesis to experimental therapeutics: lessons from completed clinical trials and a way forward. Almost all recent therapeutic clinical trials in LN assessed induction of remission, and novel drugs were evaluated by whether they improved 6- or 12-month complete and partial renal response rates compared with standard of care. Although uniformly unsuccessful, it cannot be assumed that these novel therapies do not work in LN.[25] Rather, the explanation for the failures may be found in how the novel therapies affect the pathogenesis of LN, and thus what the therapies may be expected to accomplish.

At LN diagnosis the kidney shows considerable inflammation, especially in proliferative disease. Attenuation of inflammation should be the primary focus of induction therapy in order to limit chronic kidney damage. Currently, high-dose corticosteroids are the main anti-inflammatory drugs used in LN induction regimens. Improvement in renal response rates within 6 to 12 months will require additional therapies that control inflammation. Based on the pathogenesis of renal injury in LN,[40] it may be possible to predict the type of novel interventions that could be expected to rapidly attenuate renal inflammation. Inhibiting the alternative complement pathway or proinflammatory cytokines are examples. Alternative pathway complement inhibitors are effective for experimental LN and are now available for clinical use. Given the large number of proinflammatory cytokines that appear to be relevant to LN, an interesting approach to anticytokine therapy may be blocking the activation of nuclear factor-kappaB (NF-κB), a key transcription factor necessary for the expression of several proinflammatory cytokines. Laquinimod is an anti-inflammatory small molecule that decreases NF-κB activity and has shown efficacy in murine models of LN.[43] Preliminary data from a recently completed phase 2 trial of laquinimod for LN induction demonstrated a greater improvement in kidney function and proteinuria in laquinimod-treated patients compared with standard of care alone at 6 months.[44]

Importantly, several of the novel drugs already studied in LN had presumptive mechanisms of action that targeted the processes of autoantigen presentation and the expansion of autoreactive lymphocyte clones, as opposed to inflammation (Figure 3). For example, anti-B-cell therapies eliminate antigen-presenting cells and precursors for autoantibody-producing cells. Such drugs will eventually decrease inflammation by abrogating immune complex generation and intrarenal tertiary lymphoid tissue formation, but these effects are neither immediate nor direct. Such drugs may be more effective in decreasing the chances of future LN flares, and in this way prevent the accumulation of kidney damage. In other words, such drugs may not succeed in clinical trials of induction, but may succeed in trials of maintenance of remission.

There is some evidence that drugs that attenuate autoimmunity, as opposed to inflammation, may be well suited for flare prevention (Figure 3). For example, belimumab, an anti-BlyS monoclonal antibody, was approved for the treatment of extrarenal SLE.[45] Patients with active LN were excluded from these trials. Nonetheless, patients who received belimumab had a significantly lower and dose-dependent LN flare rate than placebo patients according to a *post hoc* analysis of the trial data.[46] Similarly, the costimulatory blocker abatacept plus low-dose cyclophosphamide did not improve renal response rates at 6 months in an add-on induction trial.[47] Patients who received abatacept and achieved a complete renal response by 6 months were taken off immunosuppression and followed up for 6 more months. These patients maintained remission as well as placebo patients who had responded completely but were continued on azathioprine maintenance. Trial designs to assess drugs that attenuate autoimmunity will need to incorporate longer follow-up and a flare rate endpoint compared with induction trials.

During active LN, renal inflammation and systemic autoimmunity occur simultaneously. Induction and maintenance designations for therapy are artificial constructs. The ideal therapeutic approach would combine therapies directed toward inflammation and autoimmunity from the start in order to quickly achieve a complete renal response and maintain that response long term while minimizing drug toxicity. Future treatment paradigms should include corticosteroid-sparing anti-inflammatory drugs plus cytotoxic-sparing anti-B or T cell, or anti-type I interferon agents. Anifrolumab, a monoclonal antibody against the interferon-α receptor 1, is being tested for its effect on resolution of proteinuria in patients with proliferative LN (ClinicalTrials.Gov Identifier: NCT02547922). Anifrolumab has already shown encouraging results in non-renal SLE, especially in patients who were expressing high levels of interferon-induced genes.[48] Some novel LN drugs target inflammation and autoimmunity. For example, proteasome inhibitors kill plasma cells and block NF-κB activation and thus could directly eliminate autoreactive, autoantibody-producing cells, while simultaneously attenuating inflammation. Proteasome inhibitors have been tested in murine models of lupus nephritis and have been shown to reduce autoantibodies, glomerular expression of NF-κB, NF-κB–dependent proinflammatory cytokine levels, the degree of kidney injury, and proteinuria.[49–51] Presently, 2 clinical trials are looking at the effects of proteasome inhibitors in SLE and LN (ClinicalTrials.gov identification numbers: NCT021052594, NCT02176486).

Because proliferative LN is an aggressive inflammatory disease, early and definitive treatment has been considered crucial to preserve nephron mass. However, repeat kidney biopsies have shown a rapid accumulation of chronic kidney damage despite such treatment. Damage, represented by an increase in the NIH chronicity index from 2.8 to 4.2, was observed on biopsies done after 6 months of high-dose corticosteroids plus mycophenolate mofetil or cyclophosphamide.[27] Accumulation of damage occurs even in patients who are clinically improving. In a Hispanic cohort, the NIH

chronicity index increased from 2.6 to 3.7 in complete renal responders after induction, similar to the increase in chronicity index (2.6–4.2) found in repeat biopsies of partial and nonresponders.[52] Consistent findings were observed in other studies.[53] Thus, chronic kidney damage and nephron loss occur very early in the course of LN and in the face of broad-spectrum immunosuppression. As new LN therapeutic paradigms are being developed and tested, it may be worth considering the addition of an antifibrotic agent (when available) to an induction regimen of anti-inflammatory and immunosuppressive drugs.

Summary and perspectives

LN has numerous unmet medical needs.[54] Although its pathophysiology is beginning to be understood, significant interindividual differences exist and cannot be defined by the current histopathological categories or clinical biomarkers. In the future, genetic and molecular profiling may help to individualize risk assessment. Also, guideline-based approaches to treatment preclude personalized interventions. Current trial designs in LN may mask the potential efficacy of novel drugs. Conceptual adjustments to the way the new drugs are evaluated are required.[25] Because LN affects mostly young people, nephron loss early in life will strongly increase lifetime risk for ESRD and cardiovascular mortality. Therefore, active LN should be considered a medical emergency that requires immediate action and expert guidance to optimize long-term outcomes.

DISCLOSURE

All the authors declared no competing interests.

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