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Overview of Pathophysiology and Treatment of Human Lupus Nephritis

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Abstract

Purpose of review—Despite recent developments and treatment successes, the outcome and prognosis of patients with lupus nephritis have not greatly changed since the 1980s. This review covers the application of new concepts to the understanding of renal inflammation and the study of new pharmacologic agents to improve patient outcomes.

Recent findings—Studies have shown that the presence of anti-vimentin antibodies and T follicular helper cells in patient biopsies are associated with more severe interstitial inflammation, which has been tied to faster disease progression and onset of end stage renal disease. Additionally, data regarding the role of serum IgE anti-dsDNA antibodies in lupus nephritis by means of mediating type I interferon production by plasmacytoid dendritic cells is highlighted. Finally, a thorough review of completed and currently open clinical trials of therapeutic agents is provided.

Summary—Current management of lupus nephritis is guided almost exclusively by glomerular involvement. Based on the data provided in this review, we argue that renal tubulointerstitial inflammation is no less important and represents an overlooked feature in the current clinical approach to patients. Tubulointerstitial inflammation is driven by both adaptive and innate immune mechanisms that are still poorly understood. Studying these pathogenic processes promises to reveal new therapeutic opportunities for those lupus nephritis patients with the worse prognosis.

Keywords

lupus nephritis; tubulointerstitial inflammation; glomerulonephritis

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Introduction

Lupus nephritis (LuN) is the most common severe manifestation of systemic lupus erythematosus (SLE)(1, 2) and contributes significantly to mortality in this disease(3–5). Up to 50% of SLE patients develop LuN, which usually requires potentially toxic immunosuppressive therapies(6–8). Despite currently available aggressive treatments, up to 50% of patients progress to end stage renal disease (ESRD) within 5 years of diagnosis(9–11). This response rate has not significantly improved since the 1980s, despite the advent of new therapies(8, 12, 13). This review focuses on available therapies as well as those undergoing current clinical trial investigation. In addition, an overview of the inflammatory responses, characterizing human LuN, is provided.

Current Treatment Paradigms

Current diagnostic criteria and clinical management of LuN, as recommended by the American College of Rheumatology (ACR) and European Union League Against Rheumatism (EULAR), almost exclusively focus on glomerulonephritis(14, 15). Decision-making for the initiation of treatment, selection of a therapy regimen, and duration of treatment are dependent on the characterization of renal involvement based on the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification criteria (Table 1)(16).

In clinical practice, human lupus glomerulonephritis (GN) is treated with a regimen of induction therapy followed by additional maintenance immunosuppression. Many of the treatments under discussion in this review have not received either US or European regulatory agency approvals for the indication of lupus nephritis therapy and their use should be considered as off-label or investigational (FDA and EMA, respectively). Traditional regimens are based on the National Institutes of Health (NIH) trials, which found that glucocorticoids (GC) plus intravenous (IV) pulse cyclophosphamide (CYC) were more effective than glucocorticoids alone in LuN (all classes) (12). There is also data supporting low dose pulse IV CYC based on the Euro-Lupus (EL CYC) regimen where patients receive IV CYC 500 mg every 2 weeks for 6 doses (17, 18). Mycophenolate mofetil (MMF) is another recognized option for induction therapy. Multiple trials have demonstrated that MMF has comparable efficacy to CYC (8, 19). Additionally, in Black/mixed race patients, MMF showed higher response rates compared to IV cyclophosphamide (60.4 % vs 38.5%, $p=0.033$)(8).

After completion of initial induction therapy, maintenance therapy is generally indicated in all patients. Studies have shown that patients who are not placed on maintenance immunosuppressive therapy are at increased risk of worsening renal function, ESRD, and even death (20, 21). The ALMS study found treatment failure, renal flares, and time to rescue therapy were all significantly higher utilizing azathioprine (AZA) as compared to MMF for this indication (22). Conversely, the MAINTAIN trial (LuN class III/IV/V) found similar rates of renal flares (23) and these findings were maintained at 10 year follow-up (24). The optimal duration maintenance therapy with either agent is not clear at present. The ALE06 trial (Clinicaltrials.gov identifier: NCT01946880) is a multi-center randomized controlled trial (RCT), investigating the effects of MMF withdrawal in clinically stable SLE

patients that is presently ongoing to help answer this important clinical question. Uncomplicated class V LuN is currently treated as a special subset with different treatment recommendations based on published trials (25, 26). The ACR and EULAR both currently recommend prednisone and MMF for induction in patients with isolated class V involvement (14, 15).

As noted in the above discussion, despite current therapies, a significant proportion of patients with LuN develop ESRD. Therefore, there is an unmet need for novel therapies (11, 27–29). Tacrolimus has been studied as a potential alternative for induction therapy. Chen et al. examined 81 patients with class III/IV/V LuN who were randomly assigned to tacrolimus vs NIH IV CYC regimen plus GC(30). While proteinuria was significantly reduced in the tacrolimus group, complete response (CR) rates were comparable (52.4% vs 38.5%, $p=0.2$). A more recent study by Mok et al compared GCs combined with either tacrolimus or MMF ($n=150$) followed by AZA in Chinese patients with class III/IV/V LuN (31), and found tacrolimus to be noninferior at 6 months. Studies have also looked at combining tacrolimus with MMF. Liu et al. compared 368 Chinese patients with class III/IV/V LuN treated with GCs and either tacrolimus and MMF or IV CYC every 4 weeks for 6 doses (32). At 6 months, 45.9% in the tacrolimus/MMF group had attained CR vs 25.6% in the IV CYC group ($p<0.001$) with similar percentages of adverse events (50.3 vs 52.5%). A 2016 meta-analysis by Zhang et al. found that calcineurin inhibitors (either tacrolimus or cyclosporine) were as effective as IV CYC (5 studies) or MMF (2 studies) for LuN (class III/IV/V) (33). There is a present ongoing, multicenter, RCT investigating the efficacy of tacrolimus vs MMF for induction therapy in LuN (Clinicaltrials.gov identifier: NCT01580865)

Given their success in other rheumatic diseases, biologic therapies have also been studied as potential treatments for lupus nephritis. Rituximab (RTX), which targets CD20 expressed on B cells, has been shown to be beneficial in multiple small open label and retrospective studies (34–39). Despite these encouraging results, LUNAR - a phase III RCT - produced contradictory results (40). This trial included 144 patients with class III/IV +/- V LuN treated with either RTX or placebo plus MMF and GCs. At 52 weeks there was no difference in CR or partial response (PR) rates in the RTX vs placebo groups (56.9% vs 45.8%, $p=0.18$). In a subgroup analysis, Black patients in the RTX group were found to have a trend to higher overall response rates (OR: combined PR and CR) compared to placebo (70% vs 45%, $p=0.20$).

Despite LUNAR, studies have continued to investigate the potential use of RTX in LuN. Moroni et al. performed a clinical observational study of 54 patients with class III/IV/V LuN induced with either RTX, MMF, or CYC (41). At 3 months, renal response rates were similar among the three groups (58.8% RTX vs 63.1% CYC vs 64.7% MMF). At 12 months, CR rates were also similar between the groups (70.6% RTX vs 65% CYC vs 52.9% MMF). Although this was a small, non-controlled trial, it suggests that RTX may still be beneficial in select LuN patients.

Belimumab, which inhibits B-cell activating factor (BAFF), is an FDA-approved agent for treating non-renal SLE that is also being studied as a potential therapy for LuN. The BLISS-52 and BLISS-76 trials focused on stable, non-severe LuN and excluded patients

with acute and/or severe LuN defined as proteinuria ≥ 6 g/day, serum creatinine > 2.5 , or those on dialysis (42, 43). In a pooled analysis Dooley et al. found that although patients receiving belimumab 1 mg/kg or 10 mg/kg had decreased proteinuria compared to placebo, this difference did not meet clinical significance (median decrease: 48.3%/39.1% vs 75.2%, NS) (44). Likewise, there was no significant difference in renal flare (2.1%/1.1% vs 3%, NS) and renal remission rates (65.7%/70.5% vs 58.7%, NS) as compared to placebo. Despite this, renal improvement as measured by SELENA-SLEDAI(45), was statistically significant in patients being treated concurrently with MMF and belimumab 1 mg/kg and 10 mg/kg groups compared to placebo (52.6%/63.2% vs 27.8%, $p=0.03$). Although these studies only included patients with stable, non-severe LuN, they suggest that belimumab may be beneficial. There is a current phase III, double-blinded, RCT investigating the effects/safety of standard of care plus belimumab 10 mg/kg vs placebo in patients with LuN to address this question. (Clinicaltrials.gov identifier: NCT01639339) Another candidate biologic therapy for LuN is abatacept which is a soluble fusion protein of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and Fc immunoglobulin IgG1. ACCESS randomized patients with class III/IV+/-V LuN to weight-based IV abatacept vs placebo (46). Both groups also received GCs and 500 mg IV CYC every 2 weeks for 6 doses, followed by AZA maintenance. At 24 weeks, there was no difference in CR or OR rates in the abatacept vs placebo groups (33% vs 31% CR, 59% vs 59% OR). Adverse events were comparable in both groups. Studies have also looked at combination abatacept and MMF. A double-blind study randomized patients with Class III/IV +/- V LuN to IV abatacept 30 mg/kg through day 57 then 10 mg/kg vs 10 mg/kg vs placebo (47). Patients were also maintained on MMF and GCs. Investigators found no difference between placebo and abatacept in regards to patients who met criteria for CR or PR. There is a current ongoing phase III, double-blind multicenter RCT investigating abatacept vs placebo with background MMF and GCs over a 104-week period. The primary efficacy endpoint is the proportion of patients attaining CR based on renal function, proteinuria, urine sediment, and GC dose (Clinicaltrials.gov identifier: NCT01714817).

There have been several other recent studies evaluating novel treatments for proliferative LuN, which were terminated early due to side effects or inefficacy. Atacicept is a soluble, fully human, recombinant fusion protein, which inhibits both BAFF and a proliferation-inducing ligand (APRIL)(48). A phase II/III double-blind RCT of subcutaneous atacicept (4 patients) or placebo (2 patients) plus MMF and prednisone for active class III/IV LuN was discontinued early due to severe, rapid declines in serum IgG and serious infections in 3 out of 4 treated patients(49). Ocrelizumab, a recombinant, humanized antibody, sharing targeting of CD20 with rituximab (50), was also studied in a double-blind phase III RCT of 381 patients with class III/IV+/-V LuN (51). This study was also terminated early due to increased risk of serious infections (28.3% overall) in the ocrelizumab group. The long-term extension trial of BIIB023, a humanized monoclonal antibody against TNF-related weak induced of apoptosis (TWEAK), in class III/IV+/-V disease was also recently terminated due to inefficacy (Clinicaltrials.gov identifier: NCT01930890).

Of the possible new therapies undergoing current development, blisibimod is a BAFF antagonist that binds to both soluble and membrane-bound BAFF and inhibits the interaction of BAFF with BAFF receptor, transmembrane activator and CAML interactor (TACI), and

B-cell maturation antigen (BCMA)(52). A recent double-blind phase Ia/Ib RCT of 56/64 patients with mild/inactive lupus were randomized to receive either blisibimod SC/IV, respectively, at various doses vs placebo (53). The trial found a significant decrease in patient serum B cell counts with the study drug without an increase in adverse events. While this trial excluded patients with active LuN, there is a pending phase III, double-blind RCT to evaluate the efficacy and safety of blisibimod in patients with lupus and stable LuN (Clinicaltrials.gov identifier: NCT02514967).

Mizoribine (MIZ) is another potential novel treatment for LuN. It is thought to inhibit inosine monophosphate dehydrogenase – the same target as MMF (54). Feng et al. randomized 90 Chinese patients with active Class III/IV/V LuN to receive MIZ every other day vs MMF vs IV CYC 500mg every 2 weeks plus GC over a 24-week period (55). All three groups showed an improvement in renal responses at 12 weeks but the CYC group had more early responders compared to MIZ (96.7% vs 73.3%, $p=0.02$). At 24 weeks, CR and OR rates were similar between all groups (CR- 22.7% MIZ, 24% MMF, 25% CYC, overall response - 68.2%, 72%, 75%). An ongoing phase III non-inferiority RCT is actively recruiting patients in China to further investigate the role of MIZ vs CYC in class III/IV/V LuN (Clinicaltrials.gov identifier: NCT02256150).

Type I interferons, including interferon α , have been implicated in the pathogenesis of SLE. Anifrolumab, a human monoclonal antibody against the interferon α receptor 1(56), is currently being studied as a potential new therapy for lupus. A phase II open label trial in 17 Japanese patients with SLE showed that anifrolumab suppressed interferon gene signatures in 85% of patients at the 300 mg dose at day 169 and 95% of patients in the 1000 mg dose at day 85 without any safety signals(57). The TULIP-LN1 trial is a phase II double-blind RCT, which is currently enrolling patients to study the efficacy and safety of anifrolumab vs placebo in class III/IV +/- V LuN (Clinicaltrials.gov identifier: NCT02547922).

Finally, laquinimod (LAQ) is another promising novel therapy for LuN. Laquinimod's method of action is not fully known but it is thought to behave as an oral immunomodulatory agent by downregulating select cytokines, including IL-6, IL-12, IL-17, IL-23, and TNF α while increasing IL-10(58). In a phase IIa double-blind RCT of 46 LuN patients comparing LAQ 0.5 mg or 1 mg daily vs placebo plus MMF and GCs(58), the investigators found that renal responses were higher in the LAQ 1 mg compared to the 0.5 mg and placebo groups (62.5% vs 40% vs 33.3%) at 24 weeks. The authors note they are planning a larger study to further investigate the efficacy and safety of LAQ but no formal trials have been registered at this time.

Pathophysiology and current experimental models

As previously noted, although kidney involvement in LuN can affect either the glomerular or tubulointerstitial compartments as well as combinations thereof, most classification schemes utilized in clinical practice focus almost exclusively on glomerular pathology. Two other commonly used tools for assessing disease severity – the NIH activity and chronicity indices (59) – are likewise heavily weighted towards glomerular, as opposed to tubulointerstitial involvement (Table 2) Moreover, fibrosis and sclerosis generally contribute more to the above scoring system than inflammation in either glomerular or tubulointerstitial

compartments (Table 2)(60). A growing body of published literature supports the importance of tubulointerstitial inflammation (TII) in determining prognosis and patient outcomes(61–65). Although these studies noted an association of active TII with glomerular involvement, a multivariate analysis, performed in a large retrospective cohort of 59 LuN patients, noted that TII was an independent predictor of ESRD progression and this correlated with serum creatinine level at time of biopsy (OR 2.4, 95% C.I. 1.4, 4.3, $p=0.002$ for $GFR<60$ mL/min)(60). Interestingly, in contrast to most current mouse models of lupus and GN, TII has not been shown to be related to levels of complement, double-stranded DNA (dsDNA) or other serum autoantibodies(60, 63). Further studies of TII in animal models have been complicated by an absence of an adequate experimental model, that fully recapitulates the spectrum of tubulointerstitial involvement seen in human patients, such as germinal center formation and other features of tertiary lymphoid neogenesis (TLN)(66–68). To date, characterization of TII in humans has revealed the following common features: the presence of widely interspersed B cells and plasma cells, notably absent from glomeruli(60, 66); co-localization of B and T cells in well-formed aggregates in a majority of biopsy specimens(66); occurrence of discrete immune complex deposits within the tubular basement membrane in 50% of patients(66, 69); and the presence of T follicular helper (T_{FH}) cells in close conjugates with B cells in a significant fraction of patients, which correlated with worse renal function at time of biopsy in a retrospective analysis (mean serum creatinine/GFR by MDRD: 2.3/44.8 mL/min for T_{FH}^{+} biopsy ($n=19$) and 1.1/74.8 mL/min, for T_{FH}^{-} biopsy ($n=23$) patients, respectively; $p=0.03$)(70). The adaptive nature of the inflammatory response in TII has been further evidenced by clonal relatedness of B cell antibodies, expressed from patient biopsies(66). Analysis of the most common antibody specificities has failed to reveal *in situ* responses to common nuclear antigens such as dsDNA but, instead, had predominantly cytoplasmic reactivity (11 of 25 expressed antibodies)(71). The majority of these (10 of 11) were recently shown to bind to vimentin – an intermediate filament that is a common structural component of cells(4). In addition, many of the expressed antibodies displayed a degree of poly-reactivity and rheumatoid factor activity – a measure that may reflect the *in situ* selection environment. Of interest, high titers of these antibodies were almost exclusively seen in biopsies with the highest degree of TII. Anti-vimentin antibodies have been previously described in instances of allograft rejection with high titers predictive of graft failure, and vimentin immunization of a mouse model led to accelerated cardiac rejection(72–75). As such, an anti-vimentin response is unlikely to be specific for lupus but may reflect a general state of deregulated self-tolerance mechanisms in the context of inflammation. An intriguing possibility is whether measurement of anti-vimentin antibodies would be useful as a clinical biomarker of assessing the degree of TII involvement. To date, only anti-C1q antibodies have been prospectively validated to distinguish proliferative from non-proliferating nephritis in human patients but have not been shown to be predictive of clinical course(76).

Besides the attention paid to features of adaptive immunity in the context of TII, the study of mediators of innate inflammatory responses are also likely to be of great importance. The vast majority of antigen-presenting cells (APCs) in the kidney are not limited to B cells(77). The cortex of normal human kidneys contains a network of myeloid dendritic cells (mDC) as well as fewer numbers of plasmacytoid dendritic cells (pDCs)(78). It also contains

macrophages that have similar surface phenotypes, and possibly functions, as dendritic cells (DCs)(79). In murine models, these populations appear to actively maintain tolerance in normal tissue, limit inflammation in response to tissue damage(80–83), drive inflammation in response to ischemia, infection and ureteral obstruction(80, 84–86), and resolve inflammation to allow repair(87, 88). In NZB/NZW mice, kidneys are infiltrated with pro-inflammatory macrophages and DCs(89), and both human and murine lupus is associated with a pattern of *in situ* mRNA expression, indicative of activated APCs(90). Histologically, human LuN is associated with increased DC infiltration and chemokine expression. An increase in the pDC:mDC ratio has been associated with more severe GN(91, 92). As innate immune responses have previously been more difficult to target therapeutically, this will be an important area of future study. The recent arrival of targeted immunotherapies such as programmed death ligand-1 (PDL-1) blockade(93) may bring about an important revolution in this previously neglected area of treatment of innate-mediated autoimmunity.

A final example of the potential for cooperation between aberrant innate and adaptive responses can be seen in a recent publication, implicating the surprising role of IgE anti-dsDNA antibodies in LuN(94). In this study, the addition of minute quantities of IgE anti-dsDNA antibodies to IgG antibodies with the same specificity was shown to have a potent synergistic effect on pDC production of interferon α . The prevalence of anti-dsDNA IgE antibodies in SLE patients was noted to be markedly elevated as compared to healthy controls and patients with atopic dermatitis (95–97). The authors propose that IgE serves to synergize with and amplify the response to IgG auto-antibodies in an interferon-dependent manner. Indeed, the presence of significant IgE antibody deposits in glomeruli and tubulointerstitium was noted in a majority of biopsies studied, where they co-localized with pDCs, displaying an activated type I interferon signature. In support of the hypothesis of a potential amplification loop of aberrant *in situ* responses, the addition of IgE anti-dsDNA antibodies to *in vitro* pDC:B cell cultures lead to the marked proliferation of B cells, plasma cells, and production of IgM. This data reveals a potential novel mechanism, whereby coordination between the adaptive and innate arms of the immune response creates self-reinforcing pathogenic circuits. They also argue that elucidating precise pathogenic mechanisms is a critical first step in developing appropriate targeted therapies.

Conclusion

While great strides have been made in treating human LuN, a significant percentage of patients still progress to chronic kidney disease and ESRD with conventional treatments. While ACR and EULAR recommendations(14, 15) provide some guidance on traditional induction and maintenance regimens, given the high numbers of LuN patients who do not achieve complete remission with these therapies, current approaches may not be optimal for all patients. Although clinical trials attempt to recruit ethnically diverse patient cohorts, no large RCT to date have been powered to definitively show the superiority of one regimen over another in a particular patient subgroup. Additionally, there is little guidance on how to proceed in patients who are refractory to conventional therapies. Insights into the pathogenesis of LuN and, particularly, the contributions of innate and adaptive arms of the immune system in the context of TII, may become increasingly important in approaching patients with a poor prognosis. The development of an animal model, able to reliably

recapitulate the full breadth of human LuN, would represent an important interim step in the development and preclinical validation of appropriate therapeutic targets. In addition to developing new therapeutic agents, future prospective clinical trials need to take TII into consideration as both an important prognostic marker and a central pathogenic mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

LuN	lupus nephritis
SLE	systemic lupus erythematosus
ESRD	end stage renal disease
ACR	American College of Rheumatology
EULAR	European Union League Against Rheumatism
ISN/RPS	International Society of Nephrology/Renal Pathology Society
GN	glomerulonephritis
NIH	National Institute of Health
GC	glucocorticoid
IV	intravenous
CYC	cyclophosphamide
EL CYC	Euro-Lupus protocol cyclophosphamide
MMF	mycophenolate mofetil
AZA	azathioprine
RCT	randomized controlled trial
RTX	rituximab
CR	complete response

PR	partial response
OR	overall response
BAFF	B-cell activating factor
CTLA4	cytotoxic T-lymphocyte-associated antigen 4
APRIL	a proliferation-inducing ligand
TWEAK	TNF-related weak induced of apoptosis
TACI	transmembrane activator and CAML interactor
BCMA	B-cell maturation antigen
MIZ	mizoribine
LAQ	laquinimod
TII	tubulointerstitial inflammation
TLN	tertiary lymphoid neogenesis
T_{FH}	T follicular helper cells
dsDNA	double stranded DNA
APC	antigen presenting cell
mDC	monocytic dendritic cell
pDC	plasmacytoid dendritic cell
DC	dendritic cell
PDL-1	programmed death ligand 1

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Key points

- The clinical approach to lupus nephritis patient management centers predominantly on glomerular pathology;
- The optimal duration of maintenance therapy for lupus nephritis is currently unknown;
- Tubulointerstitial inflammation is an important determinant in at least a subset of patients and is tied to faster disease progression to end stage renal disease;
- The inflammatory infiltrate possess features of deregulated adaptive and innate immune responses, the future study of which may reveal important clues to prognosis and future therapy development.

Table 1

2003 ISN/RPS lupus nephritis classification, adapted from (16)

Class	Type
I	Minimal mesangial LuN
II	Mesangial proliferative LuN
III	Focal LuN
IV	Diffuse segmental or global LuN
V	Membranous LuN
VI	Advanced sclerosing LuN

Table 2

NIH activity and chronicity index scoring, adapted from (59)

Index	Glomerular	Tubulointerstitial	Total score
Activity Index			
Maximum Score	21	3	24
<i>Individual Components</i>	Cellular Proliferation	Mononuclear Cell Infiltrate	
	Leukocyte infiltration		
	Fibrinoid necrosis/karyorrhexis*		
	Cellular crescents*		
	Hyaline thrombi/wire loops		
Chronicity Index			
Maximum Score	6	6	12
<i>Individual Components</i>	Glomerular sclerosis	Interstitial fibrosis	
	Fibrous crescents	Tubular atrophy	

Each component in the table above is scored between 0 to 3. Items marked with * are weighted by a factor of 2 (maximum of 6 points each).