Pathogenesis and treatment of systemic lupus erythematosus nephritis

Anne Davidson[a,b] and Cynthia Aranow[a]

Purpose of review

Glomerulonephritis is a challenging complication of systemic lupus erythematosus that still results in kidney loss in up to 30% of patients. In this review we highlight the development of integrated efforts to link pathogenesis with disease definition and new therapeutics.

Recent findings

Immune complex deposition in the kidney initiates an inflammatory cascade that causes glomerular disease but there are many modulating factors including genetic predisposition, products of the innate immune system, cytokines, complement and activated cells (both renal and immune). Animal models can help dissect potential disease mechanisms but the study of multiple models will be required since there are multiple subsets of human disease. Recent therapeutic studies in humans address the distinction between therapies for remission induction and remission maintenance. Multiple studies confirm the therapeutic equivalence of mycophenolate mofetil and cyclophosphamide in induction of remission but results are still far from ideal. The next few years should see the testing of new biologic reagents in humans. Another area of interest is the search for noninvasive measures of disease and disease response.

Summary

Although there has been remarkable progress in our understanding of the immunology and phenotype of lupus nephritis current therapies have insufficient efficacy. As new therapies emerge, improved clinical design coupled with mechanistic studies will be needed to identify agents that may be effective only in some patient subpopulations.

Keywords

biologic therapies, biomarkers, cytotoxic drugs, mouse models, SLE nephritis

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[a]Departments of Medicine, Columbia University Medical Center and [b]Departments of Microbiology, Columbia University Medical Center, New York, New York, USA

Correspondence to Anne Davidson, 1130 St Nicholas Ave Room 918, New York, NY 10032, USA
Tel: +1 212 851 4571; fax: +1 212 851 4548; e-mail: ad2247@columbia.edu

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Abbreviations

CR	complete response
MCP-1	monocyte chemotactic factor 1
MMF	mycophenolate mofetil
PR	partial response
SLE	systemic lupus erythematosus
TNF	tumor necrosis factor
Treg	regulatory T-cell

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Introduction

Systemic lupus erythematosus (SLE) nephritis is characterized by immune-complex mediated glomerular and tubulointerstitial inflammation leading to chronic renal insufficiency in up to 30% of affected patients. In this review we will focus on developments in the pathogenesis and treatment of SLE nephritis published over the last 12–18 months.

Pathogenesis of systemic lupus erythematosus nephritis

It is generally accepted that SLE nephritis is initiated by the glomerular deposition of immune complexes. The precise specificity of nephrotoxic autoantibodies is unknown but several renal targets have been identified using Western blotting of mesangial cell extracts or phage display libraries [1]. These are not always reproducible suggesting that multiple specificities exist [2,3]. One small study of 37 patients shows that only a subset of autospecificities in the serum correlates with nephritis including antibodies to DNA, glomerular extracts and laminin, specificities also identified in murine SLE [4••]. Deposition of immune complexes in the kidneys, however, can occur even in the absence of anti-DNA antibodies [5,6]. The mechanism for glomerular antibody deposition has recently been reviewed [7•]. Immune complexes in the mesangium or subendothelium that contact the extravascular space appear to recruit inflammatory cells, whereas the glomerular basement membrane prevents the recruitment of inflammatory cells to the subepithelial space. The isotype of the deposited antibody also influences pathogenicity. In membranous disease antibody deposits are skewed to Th2 dominated isotypes [8] that fix complement poorly.

Renal autoantibody deposition triggers a cascade of inflammatory events. In NZB/W F1 [9], but not MRL/lpr [10]

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mice engagement of activating Fc receptors on bone marrow derived myeloid cells is required for the initiation of a glomerular inflammatory response. Complement recruitment and activation is also an early feature of SLE nephritis (reviewed by Turnberg and Cook [11••]). Inflammatory responses may be amplified *in situ* by the renal production of complement components and by the recruitment of anti-C1q autoantibodies to the sites of immune-complex and complement deposition [12]; antibodies to C1q are associated with active SLE nephritis [13,14]. Therapeutic studies in mice show that blockade of C5 retards the development of kidney disease both in the NZB/W and MRL/lpr models [15,16].

Although autoantibody deposition in the kidneys is an important pathogenic component of SLE nephritis it is increasingly recognized that signals from the innate immune system and cellular immunity also contribute to renal disease. Immune complexes directly activate resident renal cells through Toll-like receptors to produce inflammatory mediators. Cytokines can induce endothelial cells to express adhesion molecules, increasing the probability that they will recruit inflammatory cells after contact with immune complexes [17•]. Some SLE patients develop a non-inflammatory podocytopathy in which podocyte damage is mediated by soluble inflammatory mediators [18•]. In MRL/lpr mice T-cell mediated interstitial renal disease and vasculitis together with mild glomerular changes can occur even in the complete absence of immunoglobulins [19]. Microvascular damage and thromboses also occur in the setting of SLE nephritis and may be more common in patients with antiphospholipid antibodies [20•].

B-cells, T-cells, macrophages and dendritic cells are recruited into the inflamed kidney. Little is known about this process including the order in which cells appear, their activation state, their ability to proliferate *in situ*, and their presentation of or activation by renal antigens. Recent studies of remission induction in mice suggest that cellular infiltration into the kidneys is a dynamic process regulated by local chemokine production. In NZB/W mice, treatment of established nephritis with a combination of cyclophosphamide and CTLA4Ig does not alter renal immune complex deposition but does induce remission [21,22]. This is secondary to downregulation of expression of multiple chemokines in conjunction with a decrease in the number of activated lymphocytes capable of migrating to the kidney [21]. Thus the initiation of nephritis by immune complexes can be delayed if downstream effector mechanisms, that is, cell activation, migration or death, are altered. This concept offers potential new therapeutic approaches.

Both the risk and severity of nephritis are influenced by genetic polymorphisms [23•,24]. Several small studies [25–29] in the last year have reported genetic polymorphisms that associate with risk or severity of SLE nephritis. A novel association reported this year is a low copy number of the Fcγ receptor 3B with SLE nephritis. Deficiency of this receptor is associated with susceptibility to glomerulonephritis in rodents perhaps due to poor clearance of immune complexes by neutrophils [30••]. Meta-analyses testing associations of genetic polymorphisms with general SLE are underway [31,32•]. In the future, such analyses in SLE nephritis may predict the risk of renal disease and damage in SLE patients and help influence therapeutic decisions.

New clinical trials in humans

There are a number of recent reports examining the effects of therapeutic interventions for lupus nephritis but definitive double-blind placebo controlled studies are scarce. Clinical investigation of lupus nephritis is difficult as there are no universally accepted measures of renal activity, or progression, or of complete response (CR) and partial response (PR). Studies often define these outcomes differently. Recommendations to standardize the study of lupus nephritis and guidelines for the length of studies for induction and maintenance of remission have recently been published [33•]. An additional advance is the new histologic classification by the International Society of Nephrology (ISN)/Renal Pathology Society that should provide an improved framework for standardization of patient populations [34]. Two reports using the ISN classification on observational cohorts both show that classification is an accurate predictor of outcome and suggest a poorer prognosis of Class IV-S (segmental lesions) versus Class-IV-G disease (global lesions) [35••,36]. Thus, the prognostic value of an initial renal biopsy appears clear.

Non-biologic agents

Until recently the accepted standard of care for remission induction has been monthly intravenous, cyclophosphamide 0.75–1.0 g/m^2. Low dose cyclophosphamide regimens have also been effective [37]. One recent report [38] describes a low dose cyclophosphamide regimen given at fixed intervals until a CR was achieved. Although 41.9 and 21.3% of patients achieved CR and PR at 1 year, the mean cumulative dose of cyclophosphamide at 2 years was substantial, 14.1 g. Oral cyclophosphamide continues to be administered in some centers. One report of 212 Chinese patients with diffuse proliferative glomerulonephritis showed a 59% CR and 26% PR with either oral or intravenous cyclophosphamide. Better outcome correlated with the total dose of cyclophosphamide with no effect of the route of cyclophosphamide administration on renal outcome. Five, 10 and 15-year renal survival rates were 88.7, 82.8 and 70.7% [39•].

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A second report [40•] showed complete remission in 82.4% of 66 patients with DPGN treated with oral cyclophosphamide but a 39.1% rate of relapse during a mean follow-up of 91.7 months on azathioprine and prednisolone.

Insufficient efficacy and poor tolerability of cyclophosphamide have led to the evaluation of other agents for remission induction. Multiple open-label reports show that mycophenolate mofetil (MMF), a selective inhibitor of inosine-monophosphatase-dehydrogenase induces renal remission. A randomized, open-label trial of 140 patients with proliferative nephritis comparing pulse cyclophosphamide to MMF demonstrated that MMF was more effective than cyclophosphamide in achieving CR (22.5% versus 5.8%) after 24 weeks but there was no difference in PR (29.6% versus 24.6%) [41••]. Another smaller study [42•] comparing MMF to intravenous cyclophosphamide showed that CR was achieved in only 12 and 26% (NS) of 44 patients receiving cyclophosphamide or MMF respectively. A previous trial of MMF or oral cyclophosphamide in 42 patients with proliferative nephritis showed MMF to be equally effective and less toxic for induction of remission [43]. Long-term follow-up subsequently showed MMF's capability to maintain a renal response. During a median follow-up of 63 months nine of 31 patients induced with oral cyclophosphamide and maintained with azathioprine relapsed compared with 11 of 33 patients induced and maintained on MMF. There was additionally no difference in a composite endpoint of end-stage renal disease or death in either of the two treatment regimens [44••]. This is similar to previous reports comparing maintenance with MMF, azathioprine or quarterly cyclophosphamide [45,46•]. MMF and azathioprine, however, were each superior to cyclophosphamide in preventing a composite endpoint of end-stage renal disease or death. Of note, the utility of determining thiopurine S-methyltransferase genotype polymorphisms for identifying individuals at risk for azathioprine toxicity continues to be controversial. No association between TPMT genotype and toxicity was found in Korean patients with lupus [47]. Finally, there have been two reports of successful MMF treatment for membranous nephritis [48,49].

These studies in sum suggest that MMF appears at least equivalent to cyclophosphamide for remission induction with the advantage of a better safety profile, and that either MMF or azathioprine can maintain remission. Rates of remission induction are not optimal, however, and relapses continue to occur at unacceptably high rates [50,51,52•], fueling the search for better therapeutic options.

Small trials of several other immunosuppressive reagents for remission induction have been reported in the last year. These include another inhibitor of inosine-monophosphatase-dehydrogenase, mizoribine [53], tacrolimus [54] and leflunomide [55]. The efficacy and safety of these agents needs to be determined [56]. Angiotensin converting enzyme inhibitors may be adjunctive agents for lessening proteinuria in patients with lupus nephritis [57•,58,59•].

Biologic agents

Anti-tumor necrosis factor (TNF)α agents are available and widely used by rheumatologists. Their use in lupus is tempered since they exacerbate disease in the NZB/W mouse and induce antibodies to dsDNA and lupus syndromes in humans. They have even induced lupus nephritis [60]. Thus TNFα appears to protect against initiation of lupus-like diseases. TNFα is present, however, within the inflamed SLE kidney and may be a pathogenic effector cytokine. In one published report, a short course of infliximab given to six patients with active lupus (four with nephritis) decreased proteinuria within 1 week of starting therapy. Proteinuria reached at least 60% of baseline after 8 weeks. In contrast, anti-dsDNA and anticardiolipin antibody titers increased in four patients although no clinical flare or drop in serum complement occurred [61•]. The long-term efficacy and safety of anti-TNFα agents in all or a subset of lupus nephritis may be clarified in larger, long-term, randomized studies. Routine off label use of these agents should probably be discouraged until further information is available.

Intravenous immunoglobulin (IVIg) continues to be used for lupus nephritis resistant to other therapies although there are no controlled trials for this indication, probably due both to expense and relative shortage. Potential mechanisms of IVIg efficacy in SLE remain controversial. One possibility is via blockade of Fc receptors. Efficacy of the Fab'2 fragments, however, has also been reported (reviewed by Zandman-Goddard *et al.* [62] and Toubi *et al.* [63]). Removal of immunoglobulins through plasmapharesis has been previously explored as an approach to lupus nephritis and proved ineffective [64]. More recently, immunoabsorption was studied in 16 lupus nephritis patients. After 12 months of follow-up, mean proteinuria was significantly lowered and other measures of disease activity were significantly improved although not to normal or inactive levels [65].

The efficacy of B-cell depletion for lupus nephritis is unknown and a randomized double-blind placebo controlled trial of anti-CD20 (rituximab) is underway. The results of open label studies of anti-CD20 in SLE nephritis were recently reviewed [66,67••]. One intriguing observation in a small number of patients is that B-cell reconstitution following anti-CD20 antibody may be associated with loss of an autoreactive memory B cell subset suggesting a possible disease modifying effect

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[68]. It is still unclear, however, whether multiple courses of this reagent can be safely given and whether permanent deficiencies in protective responses may ensue.

Development of biomarkers for nephritis

Noninvasive measures of renal activity have become more advanced and may eventually be used to predict risk of nephritis, to detect preclinical nephritis, to act as surrogate markers for severity or histologic subtype of nephritis, or as surrogate endpoints for clinical remission, or even as markers for response to a particular therapy. Several new studies have reported potential biomarkers for lupus nephritis. Unfortunately, a uniform definition of renal disease and clinical outcome correlations are missing in most of these studies. Approaches include discovery-based methods such as microarray technology to analyze differential expression of genes in lupus kidneys [69,70•] or proteomic methods to identify urinary proteins in patients with nephritis [71•]. The limited data available so far suggest a considerable degree of heterogeneity among SLE patients (reviewed by Schmid *et al.* [72••]). A second approach uses quantitative PCR or antibodies to identify known specificities in the serum or urine. Interestingly, a relatively large study [73] showed the predominance of the Th1 transcriptional regulator T-bet over the Th2 transcriptional regulator GATA-3 in patients with active class IV but not class V glomerulonephritis, implying that the local effector response in proliferative glomerulonephritis is Th1 dominated. Several small studies of urine sediment mRNA have documented expression of a number of chemokines and cytokines, some of which decrease upon remission [73–75,76••]. Monocyte chemotactic factor 1 (MCP-1) (or CCL2) [77–79] and adiponectin proteins [80] have been identified in the urines of a subgroup of nephritis patients and MCP-1 levels decrease during remission [78,79]. In one study of 106 patients which included 49 with active nephritis, expression of MCP-1 mRNA in the urine sediment correlated with both histologic activity index and SLE Disease Activity Index [81]. In MRL/lpr mice, MCP-1 antagonism attenuates disease, supporting the notion that it is indeed a pathogenic chemokine [82]. Interestingly, soluble levels of endothelial protein C receptor, a marker for vascular injury, were found to correlate with serum creatinine in one cross sectional study [17•]. Multiplexed assays of serum and urine are currently under development (reviewed by Balboni *et al.* [83•]). With respect to urine, these studies are likely to preferentially detect proteins stable enough to survive a variable time in the bladder and that are soluble rather than membrane-bound or intracellular. Longitudinal prospective studies will be required to determine the predictive value of any markers and to assess any potential benefit over standard screening assays that detect glomerular capillary leak.

Advances in therapeutics

The development of new therapeutics for SLE is progressing rapidly as knowledge of pathogenic mechanisms increases. Potential new therapies for SLE patients were recently reviewed [84••] and will not be discussed further. Novel targets identified in the last year using mouse studies are shown in Table 1 [16,85•,86,87•,88••, 89,90•,91,92••,93••,94–99,100•,101,102,103•,104–108]. Most of these studies are preventive rather than remission inducing. It is also important to note that studies using targeted gene deletion address the relevance of a particular target with respect to disease initiation but may not necessarily predict a therapeutic effect during the effector stages of disease. Some interventions are based on depletion of particular lymphocyte subsets or antagonism of cytokines, while others such as chemokine or complement inhibitors are directed against the inflammatory response in the target organ. It is clear, however, that 'normal' trafficking of cells to target organs is protective in the absence of inflammation and may additionally be required for egress of inflammatory cells [109,110]. In addition, normal trafficking of regulatory cells may help modulate the inflammatory response. General questions remain about therapeutic strategies including whether it is possible to reduce the autoreactive response without producing systemic immunosuppression or to restore self-tolerance with a single therapeutic agent. Restoration of some aspects of self-tolerance was achieved both in Toll-like receptor (TLR)9 knockout mice [85•] and in NZB/W mice treated with a combination of CTLA4Ig and CD40L blockade [111]. In both models the autoantibody response was suppressed but responses to foreign antigen were preserved. Finally, little is currently known about the role of regulatory T-cells (Tregs) in SLE nephritis. In human SLE there appears to be a global depletion of CD4+CD25+ regulatory T-cells. An initial study of 55 patients, however, showed no differences in Tregs between patients with renal and nonrenal flares [112]. Several studies in mice address the therapeutic potential of Tregs for SLE. Depletion of Tregs accelerated renal disease in NZM2328 mice. Unfortunately, even though the anti-DNA response was suppressed upon transferring back the CD4+CD25+ T-cells, the renal disease did not reverse [113]. Similarly, transfer of exogenously expanded Tregs into NZB/W mice resulted in only modest suppression of disease [86]. In contrast, CD4+CD25+ and CD8+ regulatory T-cells induced with low doses of nucleosomal peptides in SNF1 mice [87•] or with anti-DNA immunoglobulin peptides in NZB/W mice [114] suppressed autoantibody responses and delayed the onset of nephritis. Clearly more work is needed to define the therapeutic potential of these cells in SLE nephritis.

The study of transgenic and gene targeted mice has shown that many different immune perturbations can result in an SLE-like phenotype with varying degrees of

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Table 1 New immune interventions for SLE nephritis in mouse models

Mechanism	Target	Approach	Timing	Strain	Comments
Improved disease					
Antigen specific tolerance	Laminin [91]	Inhibitory peptide	2 months	MRL/lpr	
Antigen specific tolerance	Nucleosome [87•]	Histone peptide	3 months	SNF1	Robust/induced Tregs
B cells	BAFF (BLyS) [92••]	Receptor fusion proteins	5 months or 7 months	NZB/W	robust/remission
B cells	FcRIIb [93••]	FcRIIb bone marrow	Young	NZM2410	
B cells	FcRIIb [93••]	FcRIIb bone marrow	Young	BXSB	
Chemokine	CX_3CL1 [94]	Dominant negative	2–3 months	MRL/lpr	
Chemokine	CCR2 [95]	Knockout		MRL/lpr	
Chemokine	CCR1 [96]	Small molecule antagonist	5–6 months	MRL/lpr	Very modest
Complement	C5a [16]	Anti-receptor antibody	3 months	MRL/lpr	Modest
Cytokine	PDGF [97]	Receptor antagonist	4 months	MRL/lpr	
Cytokine switch	IL-27 [88••]	Knockout		MRL/lpr	Switch to membranous
Inflammation	IB-PI3Kγ [98]	Inhibitor	2–3 months	MRL/lpr	
Inflammation	IB-PI3Kγ [99]	Knockout		IA-PI3Ktg	
Innate immunity	IFNβ [100•]	Cytokine	3 months or 5 months	MRL/lpr	robust
Innate immunity	TLR9 [85]	Knockout		B6 $FcRII^{-/-}$	Opposite in MRL/lpr
Innate immunity	TLR9 [101]	G rich DNA	3–6 months	MRL/lpr	Opposite to knockout
Innate immunity	CRP [102]	Protein	6 weeks or 4 months	MRL/lpr	
Natural autoantibodies	DNA [103•]	IgM anti-DNA Ab	4 months or 6 months	NZB/W	
Tregs	CD4 cells [86]	Exogenously expanded	Prediseased	NZB/W	modest
Worsened disease					
Angiogenesis	VEGF [104]	Anti-receptor antibody	2 months	NZB/W	
Innate immunity	TLR9 [90•]	Knockout		MRL/lpr	
Innate immunity	DC [105]	Necrotic DC	1–3 months	MRL/lpr	
Innate immunity	TLR3 [106]	Poly I:C	4 months	MRL/lpr	
Innate immunity	TLR7 [107]	Imiquamod/ssRNA	4 months	MRL/lpr	
Innate immunity	IFNα [89]	Receptor knockout		MRL/lpr	Opposite in NZB/W
Innate immunity	IFNα [108]	Cytokine	3 months	NZB/W	

BAFF (BLyS), B lymphocyte stimulator; FcR, Fc receptor; CX_3CL1, fractalkine; CCR, chemokine receptor; PDGF, platelet derived growth factor; IB-PI3Kγ, PI3 kinase gamma IB; TLR, Toll-like receptor; CRP, C reactive protein; VEGF, vascular endothelial growth factor; DC, dendritic cell.

renal involvement and varying rates of progression to end stage renal disease [23•,115]. These studies emphasize that the balance between immune cell activation and survival is crucial for maintaining self-tolerance and preventing autoimmunity. The various spontaneous mouse models of SLE also have different immunologic profiles. For example, the proliferative kidney disease of MRL/lpr mice is associated with high levels of the Th1 cytokine IFNγ [116]. Interestingly, downregulation of IFNγ as a result of IL-27 deficiency does not abrogate disease but switches the renal immunoglobulin deposits to the Th2-like IgG1 isotype and the renal disease to a pure membranous phenotype [88••]. In contrast, high levels of the Th2 cytokine IL-4 are associated with sclerotic disease in the NZM2410 mouse [116]. Not surprisingly therefore, striking differences in responses to immunologic interventions have been observed in different mouse models. For example, deletion of the IFNα receptor prevents SLE in the NZB/W mouse [117] but worsens end organ disease in the MRL/lpr mouse [89]. In the B6.Sle2 mouse B-cell hyperreactivity is associated with low levels of type I interferons and is reversed by administration of type I interferon [118]. In contrast, IFNα accelerates disease in the NZB/W mouse [16]. Deletion of Fc receptors is protective in NZB/W mice [9] but not in MRL/lpr mice [10]. Similarly, TLR9 deficiency is renal protective in C57BL/6 FcRII deficient mice [85•] but worsens end organ disease in MRL/lpr mice [90•]. These differences among the mouse models parallel the emerging appreciation of heterogeneity in human SLE and point to the complexity of applying new treatments to diverse human populations. These studies also suggest that multiple animal models will be needed to study responses to new therapies and to dissect pathogenetic mechanisms of SLE nephritis. Investigation of multiple animal models may also anticipate potential problems in human clinical trials.

Conclusion

Despite recent advances, treatment of SLE nephritis remains a challenging clinical problem. Barriers to trials for induction and maintenance of renal response remain formidable. Given the variability of disease among SLE patients and the molecular heterogeneity observed in renal biopsies, even those with comparable histology, therapeutic interventions are likely not be successful in all patients and careful consideration will need to be given to trial design, especially the application of post-hoc analyses [119••]. Animal models allow intensive study of disease mechanisms and afford an opportunity to test potential therapeutics. Multiple models must be evaluated, however, in order to fully understand the full heterogeneity of disease mechanisms. There is an urgent need for an improved understanding and definition of the phenotype of human lupus nephritis based on clinical, histologic, immunologic, genomic and proteomic approaches. As human clinical trials proceed, these phenotypes need to be linked prospectively to responses to therapeutic

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intervention. Such an endeavor will require an intense and organized effort by all involved but will result not only in improved understanding of pathogenetic mechanisms but in treatments tailored for the many subsets of lupus nephritis.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 567).

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