Lupus nephritis: To biopsy or not to biopsy

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INTRODUCTION

Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE) with significant morbidity and mortality. LN is clinically evident in 50% - 60% of patients with SLE, but histologically evident in the majority of lupus patients. Regular monitoring of kidney function and urinalysis are crucial, because early diagnosis and intervention in LN may improve renal survival.

The traditional approach when a patient with SLE presents with proteinuria, worsening renal function and / or hematuria with or without red blood cell casts, is to perform a kidney biopsy.

To biopsy

Studies have demonstrated that SLE patients with low levels (< 1g) of proteinuria or even without evidence of kidney involvement may indeed have mild or even severe LN [1]. Based on these observations, the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association [EULAR/ERA-EDTA] and the American College of Rheumatology (ACR) strongly suggest performing a renal biopsy in patients with SLE who develop at least 500mg/24h proteinuria. However, some authorities have suggested that renal biopsy indications should be expanded to include even lower grades of proteinuria overcoming this selection bias [2].

A patient with SLE that develops kidney disease may not necessarily have LN, and other, more or less common etiologies might be responsible for renal disease. To this end, a kidney biopsy certainly serves a good purpose for the differential diagnosis of kidney involvement in patients with SLE. Cases of non-immune complex-mediated glomerulonephritis have been reported in patients with SLE [3]. Although focal segmental glomerulosclerosis was the most common finding, other entities such as thin basement membrane disease, amyloidosis, IgM nephropathy and renal thrombotic microangiopathy have also been reported. It is straightforward that patients with SLE and comorbidities, such as diabetes mellitus or arterial hypertension, may also develop lupus-unrelated renal disease.

A renal biopsy may prognosticate the long-term renal function, even though studies have shown that the risk of end stage renal disease (ESRD) is as high as 26% after 15 years in patients with LN, despite successful management. ESRD risk is higher in patients with class IV LN, but lower in patients with class V LN (15-year risk: 44% and 20%, respectively). A study demonstrated a significant association between a chronicity index ≥ 5 and the existence of cellular crescents in ≥ 30% of the glomeruli (in a repeated renal biopsy) with a persistent doubling of serum creatinine level in patients with LN with a median follow-up of 10.5 years [4]. It is generally believed that the chronicity but not the activity index is well-correlated with long-term renal function prognosis.

Kidney biopsy results can also guide treatment decisions. It is only with the use of a kidney biopsy that class switching, a less common occurrence during flares, can be identified. Pathological class transformation during renal flares was found to be more frequent in patients with non-proliferative LN (class II and V) compared to those with proliferative LN (class III and IV) in their initial kidney biopsy [5]. Thus, repeat kidney biopsies during LN flares may result in a modification of the immunosuppressive treatment employed, either by strengthening it in the majority of patients, or less frequently by reducing it.

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Not to biopsy

It has been proposed that induction treatment with mycophenolate mofetil (MMF) should not be delayed until the kidney biopsy results are available, because the majority of patients with lupus nephritis respond to this standard therapy [6]. Thus, it could be suggested that a renal biopsy might be performed only in patients that do not respond to the initial standard-of-care treatment.

Sometimes the kidney tissue obtained through a kidney biopsy is inadequate, causing difficulties and delays in the management of patients with kidney disease. An analysis of a total of 123,372 renal biopsies performed by more than 2500 nephrologists in the US illustrated a significantly increased miss rate from 2% in 2005 to 14% in 2020 [7]. The miss rate was reportedly markedly lower for nephrologists compared to radiologists. It is however disappointing that the operator gain of experience does not improve over time.

A renal biopsy is a procedure that is not devoid of risks. An analysis of 5304 kidney biopsies revealed 400 major adverse events in 273 patients (5.1%) [8]. The most frequent was a ≥2g/dL reduction of hemoglobin levels. Less frequent events include: macrohematuria, red blood cell transfusion, clinically relevant hematoma, arteriovenous fistula and the need for an invasive post-biopsy procedure. Risk factors associated with a higher bleeding risk included: increased serum creatinine levels, liver disease, a higher number of needles passes and lower levels of proteinuria.

The purpose of histological classification of LN is to treat patients according to the results of a renal biopsy. However, the distinction between focal (e.g., 45% of glomeruli affected) vs. diffuse glomerulonephritis (e.g., 55% of glomeruli affected) should probably not raise major concerns regarding our therapeutic decisions. Furthermore, neither worsening of renal function, or improvement, or even stabilization, seem to be different in patients with segmental vs. those with global proliferative LN [9]. In addition, repeat renal biopsies failed to demonstrate differences between patients with LN receiving azathioprine and those receiving the standard-of-care MMF as a maintenance therapy [10].

Another potential disadvantage of the histologic LN classification is that the currently used classification does not include tubulointerstitial lesions that may exist independently of the glomerular involvement in patients with LN. This is important, because the degree of interstitial inflammation has been reported to be strongly correlated with the rate of worsening of renal function [11]. Moreover, the risk of ESRD is higher in patients with interstitial fibrosis and tubular atrophy compared to those without [12]. Histological evidence of vascular injury has also been reported to be associated with ESRD risk, even though this association was poor in cases of proliferative LN.

As stated above, the results of a baseline renal biopsy may not be the gold-standard to predict the long-term renal outcome. A novel biopsy index consisting of a Glomerular Activity (GAI), Tubulointerstitial Activity (TIAI), Immunofluorescence (IFI), and Chronic Lesion (CL) indices has been developed, exhibiting better correlations with long-term renal outcome parameters compared to the widely used National Institutes of Health Activity and Chronicity Indices (AI and CI) [13]. According to the results, neither the standard AI and CI, nor the overall biopsy index was found to be predictive for the doubling of serum creatinine 10 years later.

A disappointing discordance between clinical renal responses and histological responses, as seen in renal biopsies performed at six months or even at 40 months after induction treatment, has been demonstrated in several studies [14,15]. It is not unusual that histological activity may persist despite complete clinical renal remission, and conversely, clinical disease activity may persist when there is no evidence of histological activity.

Novel non-interventional approaches

Dealing with the need for a regular assessment and re-assessment of the LN response to treatment, non-invasive approaches of the renal pathology are needed and are currently under investigation. Single and panel biomarkers reflecting underlying renal pathology are summarized in Table 1.

Liquid biopsy is another promising approach employed to overcome the handicaps of a renal biopsy. Liquid biopsy is non-invasive compared to the renal biopsy procedure. Test results of a liquid biopsy could be typically available much earlier than those of renal biopsy histology. The ease in frequency of a liquid biopsy offers an important advantage over the standard kidney biopsy. Furthermore, a liquid biopsy is not associated with adverse events and is usually much less costly than a standard renal biopsy.

Long non-coding RNAs (lncRNAs) regulating the expression of different genes are stable molecules found in human plasma. Transcriptomic analysis of blood samples of patients with LN identified lncRNAs as potential biomarkers of disease activity [18]. Machine-learning

Table 1. *Biomarkers reflecting kidney pathology in patients with LN.*

			References
	Urine biomarkers		
VCAM-1	Associated with AI Increased in class IV LN	P = 0.05 P = 0.02	[21]
CXCL-16	Increased in class IV LN	P = 0.04	[21]
miR-29C	Inversely correlated with CI	P = 0.001	[22]
Angiostatin	Differentiates active from inactive LN	P < 0.0001	[23]
Citrate	Higher concentrations in Class III and IV, lower in Class V LN	P < 0.05	[16]
Taurine	Absent in class III or IV LN, but normal in class V LN	P < 0.01	[16]
	Serum biomarkers		
Anti-C1q autoAbs	Associated with necrosis and crescents	Negative predictive value 100% for necrosis and 86% for crescents	[24]
	Panels		
sCr + uMCP1	Associated with different levels of interstitial inflammation	Negative predictive value 100%	[17]
uCP + PCR	Associated with different levels of interstitial fibrosis	Negative predictive value 85%	[17]
MCP1 + AAD + CP + PCR	Differentiates an AI <7 from an AI ≥7	AUC = 0.85	[17]
MCP1 + NGAL + GFR	Discriminates a CI < 4 from a CI ≥4	AUC = 0.83	[17]
MCP1 + AAG + GFR + C4	Diagnostic for membranous LN	AUC = 0.75	[17]

Abbreviations: VCAM-1: vascular cell adhesion molecule-1; CXCL16: chemokine (c-x-c motif)ligand 16; sCr: serum creatinine; anti-C1q autoAbs: autoantibodies against complement component C1q; AAG: α (1)-acid glycoprotein; NGAL: neutrophil gelatinase-associated lipocalin; uMCP-1: urine monocyte chemotactic protein 1; uCP: urine ceruloplasmin; GFR: glomerular filtration rate; PCR: protein: creatinine ratio; C4: complement component 4; AI: activity index; CI: chronicity index; LN: lupus nephritis; AUC: area under the curve.

analysis of a large whole blood RNA-sequencing dataset of patients with SLE (employing murine kidney-specific genes as disease predictors) helped to discriminate SLE patients with LN from those without LN [19]. Proteome analysis in urine samples revealed proteins that are specifically increased in patients with SLE compared to healthy individuals. Further attempts aim to illustrate potential associations of such proteins with proteinuria as well as with a prediction of a response to treatment agents employed [20].

CONCLUSION

In conclusion, it has been suggested that the everyday clinical practice strategy of MMF or low-dose intravenous cyclophosphamide administration as the initial treatment of proliferative and membranous LN, might limit the necessity for the results of a renal biopsy as the leading option among the therapeutic decisions in patients with LN. The results of a renal biopsy are of limited value in assessing a treatment response and may not predict accurately enough the long-term renal survival. Some authors have proposed omitting a baseline biopsy, initiating standard-of-care- treatment and performing a kidney biopsy later on, to assess the response to treatment. Finally, less invasive strategies are under development and evaluation, based on the isolated or the combined use of circulating and/or urinary biomarkers in order to replace the invasive renal biopsies, allowing in addition for a close monitoring of LN activity and disease progression.

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