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## **Lupus nephritis: Is it necessary to systematically repeat kidney biopsy?**

### **Néphropathie lupique : Faut-il systématiquement effectuer une biopsie rénale de contrôle ?**

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#### **Editorial**

**KEYWORDS:** Lupus Nephritis, Kidney Biopsy, Repeat biopsy, Relapse, Lupus flare, Proteinuria

## Introduction

Lupus nephritis (LN) is a frequent complication of systemic lupus erythematosus (SLE) [1], with a prevalence ranging from 29 to 82% of patients with SLE, depending on their ethnicity [2]. In SLE, LN is associated with increased morbidity and mortality. A single flare of LN can lead to significant loss of podocytes and nephrons, which can accelerate the aging-related nephron loss [3] and the onset of chronic kidney disease (CKD). Approximately 10 to 20% of SLE patients with LN will develop end-stage kidney disease (ESKD) after 10 years [4,5], with the worst risk for patients with diffuse proliferative (class IV) LN (5).

In case of suspicion of LN (especially in the presence of persistent proteinuria  $\geq 0.5$  g/24h or 0.5 g/g of creatinine), a kidney biopsy (KB) is performed to confirm and grade the severity of kidney involvement [1,6,7]. This will guide the therapeutic strategy [8,9]. After the treatment of a flare of LN, indications and timing of repeat KB are debated.

According to the 2019 EULAR Guidelines, repeat KB can be considered in case of non-responsiveness to immunosuppressive treatment, or in case of relapse [9]. The 2021 KDIGO recommendations also state that the use of repeat biopsies may help managing the duration of immunosuppression [8]. Indeed, another potential interest of repeat KB is the assessment of pathological remission in patients for whom immunosuppressive therapy weaning is being considered [10]. However, KB remains an invasive procedure, with a prevalence of bleeding complications of 5% [11]. Therefore, the benefits/risks balance of the indication of KB must be precisely evaluated, especially in patients with impaired kidney function who display an increased bleeding risk [12]. In addition, patients' willingness to undergo multiple KB can be a limiting factor.

We will describe here three situations: repeat KB for non-responsiveness to immunosuppressive treatment, repeat KB for suspicion of relapse of LN, and repeat KB for the personalization of therapy.

### **Repeat kidney biopsy for lack of response to treatment (refractory LN)**

After an induction therapy for LN, complete clinical response is defined in Europe as a proteinuria below 0.5-0.7 g/day (or urinary protein/creatinine ratio (UPCR) below 0.5-0.7 g/g), associated with normal or non-deteriorating kidney function (within 10% of baseline estimated glomerular filtration rate (eGFR)) [9]. Partial response is defined as a reduction  $> 50\%$  of UPCR (or non-nephrotic range proteinuria in patients who were previously nephrotic), and normal or non-deteriorating eGFR. The threshold of 0.7 g/day after 12 months of treatment has been shown to be predictive of long-term kidney outcome in LN [13], and an important reduction of proteinuria is associated with better long-term kidney outcome [14].

In case of lack of response to treatment, or insufficient response, repeat KB can distinguish persistent active lesions from chronic damage which can also be responsible for persistent proteinuria or eGFR impairment. On the one hand, the presence of persistent active lesions confirms refractory LN, and can require immunosuppressive therapy intensification, provided that compliance to treatment has been verified [8,9]. On the other hand, chronic damage can also be responsible for persistent proteinuria, but therapy then relies on nephroprotective drugs.

The optimal timing for repeat KB in this case remains to be determined, and when LN should be considered refractory is still a matter of debate [15]. The 2012 EULAR/ERA-EDTA guidelines defined refractory LN as failure to improve within 3 to 4 months, absence of partial remission after 6 to 12 months, or absence of complete remission within 2 years [16]. The 2020 EULAR/ERA guidelines [9]

proposed that a 25% reduction in UPCR should be obtained after 3 months, followed by a 50% reduction of UPCR after 6 months, and < 0.5-0.7 g/g after 12 months. So, the clinical definition of refractory LN could be not to reach those targets. Yet, these recommendations also state that proteinuria kinetics are important to define refractory LN, and that decreasing proteinuria (even if targets are not met) could justify further waiting, especially in patients with nephrotic-range proteinuria at baseline, provided that kidney function is stable.

Several studies found significant discordance between clinical remission and histological lesions on KB. Zickert *et al.* found that 8 months after an induction immunosuppressive treatment, 48% of the patients were non-responsive and 27% partially responsive, and that 61% of patients with partial clinical response still displayed active lesions on repeat KB [17]. Whether treatment should be intensified in patients who are in clinical remission but still display pathological active lesions is unknown, and once again the evolution of lesions (improvement, stability or worsening) should probably be considered.

Following a LN flare, class switch can occur in up to 40%-50% of patients, typically from non-proliferative classes (class II or V) to proliferative classes (class III or IV with active lesions) [18,19], worsening the kidney prognosis and often requiring an increase in immunosuppressive therapy. Repeat KB can also allow the detection of this class switch in patients who do not evolve as expected.

### **Repeat kidney biopsy for suspicion of LN relapse**

LN relapse must be suspected in case of a reappearance of a UPCR > 0.5 g/g in a patient who had reached complete remission, in case of an increase in UPCR in a patient with a chronic residual proteinuria, and/or in case of declining kidney function. Identifying rapidly the onset of a LN is essential to avoid the installation of irreversible kidney damage which can impact long-term kidney prognosis.

KB remains a very important procedure to confirm a relapse of LN. Indeed, routine exams like serum creatinine, proteinuria, or immunological markers are usually insufficient to distinguish between new active lesions and the evolution of chronic damage related to LN itself or to vascular (smoking, hypertension, anti-phospholipids...) or metabolic (diabetes, obesity) associated conditions. To date, non-invasive biomarkers like urinary peptides [20] have been poorly correlated with the presence of active lesions. Non-invasive biomarkers of lupus activity remain an important field of research.

Repeat biopsy can also highlight a differential diagnosis, which will change the treatment strategy. Approximately 40% of patients with SLE display antiphospholipid antibodies (aPLs), but less than 40% of them will display thrombotic events. Patients with SLE and antiphospholipid syndrome (APS) have a worse long term kidney outcome compared with patients with SLE only [21]. 2019 EULAR Guidelines suggest that all patients with SLE should be tested for aPLs, especially those with suspected LN. APS must particularly be suspected when KB retrieves vascular lesions, especially thrombotic microangiopathy (although non-pathognomonic). In case of APS-associated nephropathy, antiplatelet agents or anticoagulants are recommended [9], as well as an early introduction of renin-angiotensin system inhibitors [22]. More rarely, a drug-related acute kidney injury can clinically mimic a LN relapse, related for instance to non-steroidal anti-inflammatory drugs, fludione or calcineurin inhibitors. Exceptionally, proteinuria can be related to a pseudo-Fabry disease related to hydroxychloroquine toxicity (phospholipidosis of podocytes, with laminated “zebra body” inclusions on electron microscopy), which can be reversed after hydroxychloroquine withdrawal [23].

## Repeat kidney biopsy to adjust the treatment

Several teams have performed protocol repeat KB to adjust early the treatment of LN. Once again, clinical phenotype was poorly related to histological findings. Low levels of proteinuria (0.2 to 0.5 g/g) can be associated with proliferative LN [24]. After 6 months of induction immunosuppressive treatment, 39 to 62% of patients with complete clinical remission still had active lesions on repeat biopsies [17,25]. Parodis *et al.* found that in patients with biopsy-proven active proliferative LN undergoing per-protocol repeat biopsies, high National Institute of Health (NIH) Activity Index scores on the repeat biopsy were associated with an increased probability and shorter time to kidney relapse [26]. Tubulointerstitial inflammation, interstitial fibrosis/tubular atrophy and high NIH Chronicity Index scores were associated with worse sustained kidney function [17,25,26]. Chronic renal damage increased in the second biopsy even in patients with complete clinical response [25].

In patients with protocol KB performed during clinical remission, repeat KB could predict the risk of LN flares. In a prospective study assessing the interest of protocol repeat biopsies, De Rosa *et al.* found that LN flares occurred in 11/36 patients, of which 10 had residual histologic activity on the second KB performed during remission, and all patients with an NIH activity index > 2 flared [27].

In membranous lupus nephritis, Zickert *et al.* found that resorption of deposits on protocol repeat KB was associated with clinical response, especially in patients who received Rituximab [28].

Malvar *et al.* evaluated a KB-based strategy of maintenance immunosuppression in patients with class III-IV LN. Immunosuppressive treatment was withdrawn if no active lesions were found in KB or continued if active lesions persisted. This strategy was safe, with no KB-related severe events, and was associated with a low relapse rate (7/75 patients over 50 months) [29].

The WIN-Lupus trial was the first randomized controlled trial on maintenance immunosuppressive therapy weaning after proliferative LN [10]. The non-inferiority of treatment discontinuation after 2-3 years was not demonstrated, and patients from the discontinuation group were more likely to present a severe flare of SLE (LN or extra-renal flare) during the 24-month follow-up. Higher baseline UPCR was a risk factor for LN relapse in this study. Remission was assessed only clinically in patients included in this cohort, and the interest of pathological assessment of remission, with a repeat KB to allow immunosuppressive therapy progressive weaning, was suggested.

So far, no recommendation imposes to systematically repeat KB in patients with LN, but a strategy of KB-based treatment adaptation could be an interesting option, especially in patients willing to discontinue or modify their immunosuppressive regimen, for instance for a pregnancy, in patients with side effects related to immunosuppressive therapy, difficult compliance, or atypical evolution. However, patient's choice and the risks of bleeding inherent to this invasive procedure need to be considered.

## Conclusion

Kidney biopsy remains the cornerstone of initial diagnosis and treatment guidance in lupus nephritis. Kidney biopsy often needs be repeated in case of suspicion of refractory LN before increasing treatment intensity. It is also very valuable in case of suspicion of LN relapse, especially to differentiate active lesions from the progression of chronic damage or differential diagnoses. Protocol repeat kidney biopsy, to adjust immunosuppressive therapy and possibly allow treatment weaning, may also become more and more used in the coming years (**Figure 1**). The impact of such strategy on long-term kidney outcomes still needs to be confirmed.

### **Conflict of interest statement**

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Figure 1 was created with Biorender.com (2022).

### **Figure legend**

#### **Figure 1: Indications of repeat kidney biopsy in lupus Nephritis.**

LN: Lupus Nephritis.

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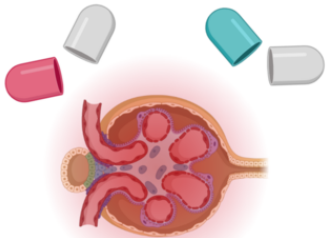
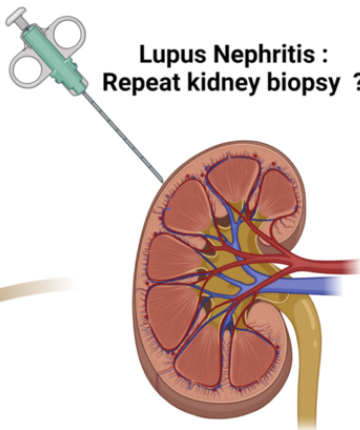
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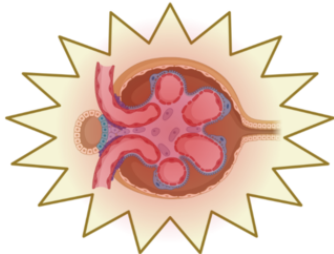
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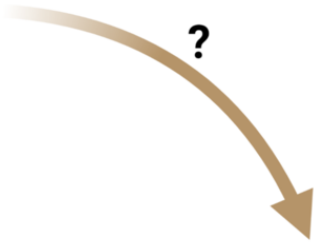
**Lupus Nephritis :  
Repeat kidney biopsy ?**



**Refractory LN**



**Suspicion of LN  
Relapse**



**Protocol Biopsy to  
adjust the treatment**