Repeated Renal Biopsy – A Predictive Tool to Assess the Probability of Renal Flare in Lupus Nephritis

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Key Words

Lupus nephritis · Repeated renal biopsy · True or apparent remission

Abstract

Background: How one responds to treatment of lupus nephritis (LN) is based on clinical features, but the activity in renal biopsy (RB) is uncertain. We have described the therapeutic decisions after performing a repeated RB on the assessment of response to intravenous cyclophosphamide (IC) and the possible prognostic role of this repeated RB.

Methods: Clinical, laboratory and histological features at the initial RB and repeated RB were analyzed in 35 patients.

Results: Data in the initial versus the repeated RB were serum creatinine 1.23 ± 1.08 and 0.96 ± 0.45 mg/dl ($p < 0.05$), glomerular filtration rate <60 ml/min in 12 and 5% patients and proteinuria 4.1 ± 2.8 vs. 0.6 ± 1.1 g/day ($p < 0.05$). Significant differences were detected in hematuria, nephrotic syndrome and serological immune features. Complete renal remission was reached in 60% ($n = 21$) at the time of the repeated RB, partial remission in 31.4% ($n = 11$), and no response IC in 8.6% ($n = 3$). Nine patients showed proliferative forms in the repeated RB, 3 of them had proteinuria <1 g/day. Just after the repeated RB, 34.3% increased or

started a new immunosuppressive therapy, 17.1% remained with the same complementary IST, and 14.3% decreased or stopped it. In the follow-up post repeated RB, 34.5% without active lesions showed a renal flare versus 77.8% with active lesions ($p = 0.04$). The mean time was 120 and 45 months, respectively. **Conclusion:** A repeated biopsy in LN distinguishes patients in true remission from those in apparent remission. By doing this, we can identify patients who could benefit from intensified treatment and for whom unnecessary treatment methods can be modified or eliminated.

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Introduction

The incidence of lupus nephritis (LN) was 16% at the time of diagnosis of systemic lupus erythematosus (SLE) and 39% throughout the evolution [1], with a negative impact on survival, but in more than 80% of these patients, LN was present at the time of enrolment [2]. Although the mortality of SLE has improved, renal survival patterns in LN over the past decades remain unchanged [3].

There is agreement that renal biopsy (RB) is essential to establish the diagnosis and propose treatment methods

[4]. However, the assessment of response to treatment is based on clinical and laboratory features, and the definitions of response are varied in several guidelines [5–7]. New data pointed out that patients with LN may have inflammatory activity in the renal tissue without clinical signs of renal involvement or despite apparent good clinical response to therapy [8, 9].

Repeated RB after immunosuppressive treatment may be important to distinguish patients in histopathological remission (true remission) of those in apparent remission, identifying patients who may need intensified therapy. Despite this data, there is no consensus about the need to repeat RB to assess the response to immunosuppressive treatment [5–7, 10].

The objective of this study was to describe the therapeutic decisions after a repeated RB, taking into account the clinical and histopathological changes after treatment with intravenous cyclophosphamide (IC). This analysis also aimed at assessing the possible prognostic role of this repeated RB.

Subjects and Methods

Patients

We retrospectively reviewed the database of Departments of Autoimmune Disease and Nephrology of Hospital Clinic, Barcelona, from 1990 to 2009 to identify patients with LN class III or IV that were treated with an induction regimen of IC and in those repeated RB was performed. All the patients fulfilled at least 4 of the American College of Rheumatology (ACR) criteria for the diagnosis of SLE at the time of kidney biopsy. Patients without histological confirmation of LN or without induction therapy with IC were excluded. The decision to perform a repeated biopsy and the time that it had to be performed were based on clinical judgment and not on an established protocol.

The Barcelona Clinic hospital's Ethics Committee approved the study protocol under the number 2016/0133.

Clinical and Laboratory Variables

The following clinical and serological data from each patient were collected from the medical records: age, gender, duration of SLE (time from the diagnosis of SLE to initial RB), time from the first IC pulse to repeated RB, hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg), albumin and cholesterol serum levels, anti-double-stranded (ds) DNA antibody, C3, C4 and CH50, lupus anticoagulant, IgG anti-cardiolipin (aCL) antibodies and IgM aCL antibodies.

Renal evaluation included urinary sediment and investigation of 24 h urine protein excretion. Hematuria (presence of ≥ 5 red blood cells per field (100 $\times$) in an isolated urine sample at least in 2 determinations), proteinuria (presence of ≥ 0.5 g/dl of protein in 24 h at least in 2 determinations), and nephrotic syndrome (urinary protein level >3.5 g/24 h, albumin serum <30 mg/dl and low-density lipoprotein cholesterol >200 mg/dl) were all assessed.

Renal function was determined by the serum creatinine (mg/dl) level and by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula [11]. Chronic kidney disease was defined as a condition when eGFR <60 ml/min [12].

Clinical and laboratory features at the time of initial RB and repeated RB were analyzed and compared.

Treatments

Treatment methods with intravenous pulses of cyclophosphamide, steroids, another immunosuppressive treatment, anti-malarial drugs, and inhibitors of the renin-angiotensin system were recorded.

Definition of Renal Response and Relapse

Response was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO)-Practice Guideline [7] and the Consensus document from the Systemic Autoimmune Disease Group of the Spanish Society of Internal Medicine and the Spanish Society of Nephrology [10] on the terminology used in the management of LN. A complete response (CR) is defined as non-active urinary sediment with proteinuria ≤ 0.5 g/day and normal or stable renal function (whether GFR was normal or not, a greater variation than 15% of normal of the filtrate was previously altered). Partial response was defined in patients with baseline proteinuria <3.5 g/day, reduction of proteinuria in $>50\%$ in comparison with the initial, and as decrease in proteinuria <3.5 g/day in patients with nephrotic syndrome. In both situations, inactive sediment and stabilization or improvement ($\pm 25\%$) in GFR with respect to initial values were needed.

We conclude that there is an 'established kidney damage' when there is the presence of an eGFR ≤ 50 ml/min and/or proteinuria ≥ 3.5 g/24 h maintained for 6 months and/or end-stage renal disease (ESRD) with or without replacement therapy as established in Systemic Lupus International Collaborative Clinics Damage Index [13].

For each patient, the duration of follow-up was considered to be the time from repeated RB to the last medical visit. In addition, the development of renal failure, ESRD requiring dialysis or renal transplantation, and death were also recorded.

Relapse or renal flare was defined based on the suggestions of the guide KDIGO [7] and the Spanish consensus [10], by the presence of glomerular hematuria (<5 to >15 red blood cells per field), deterioration on renal function (if baseline creatinine is: <2 mg/dl, an increase of 0.2 mg/dl; or if >2 mg/dl, an increase of 0.41 mg/dl), or increase in urinary albumin/creatinine ratio (if baseline <500 mg/g, an increase to $\geq 1,000$ mg/g, if baseline 500 – $1,000$ mg/g, an increase to $\geq 2,000$ mg/g, if baseline $>1,000$ mg/g, an increase of $\geq$ twofold).

Histological Features

Retrospective evaluation of RB was performed using the original slides processed for routine conventional light microscopy. Specimens were fixed in Bouin or buffered formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin, periodic acid-Schiff, Jones' methenamine silver and Masson's trichrome. Immunofluorescence results were retrieved from the original reports.

Each biopsy sample was retrospectively evaluated by a pathologist who was blinded to the status and management of the patient;

Table 1. Demographic features of the 35 patients with LN

	n = 35
Age, years	31.7±12.3
Gender, female	32 (91)
Time from SLE diagnosis to initial RB, months	42.6±52.8
Time from first intravenous cyclophosphamide pulse to repeated RB, months	30.5±9.3
Follow up from repeated RB, years	9.2±6.4

Values of categorical variables are the number and percentage of patients for whom continuous variables are presented as mean ± SD.

evaluation was done according to the World Health Organization (WHO) classification of LN when the biopsy was performed before the year 2003, and according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of LN after that date. If biopsy specimens were classified according to the WHO classification, they were reassessed according to the ISN/RPS classifications, and the new classification was compared between successive biopsies. Specimens were evaluated to understand the degree of interstitial cellular infiltration, tubular atrophy, interstitial fibrosis, and nephroangiosclerosis. The interstitial cellular infiltration was assessed as negative (–) when no cells were seen; positive (+) when cellular infiltration was mild; ++ when cellular infiltration was moderate; +++ when cellular infiltration was severe. The tubular atrophy, interstitial fibrosis and nephroangiosclerosis were assessed as negative (–) when absent; + when less than 25% of the tubuli, interstitium or vessels were affected; ++ when the lesion was between 25 and 50%, and +++ when the lesion affected more than 75% of tubuli, interstitium or vessels. Activity (0–24) and chronicity (0–12) indices from each biopsy sample were assigned [14].

Antiphospholipid antibodies-associated nephropathy consists of whole renal vascular involvement. Histological findings are thrombotic microangiopathy, which basically represents an acute event. Other lesions constitute fibrous intimal hyperplasia, fibrocellular arterial occlusion, focal cortical atrophy and thyroidization tubular reflect chronic renal damage [15].

Statistical Analysis

Quantitative variables were described using mean and SD, except the renal flare-free after repeated RB that is expressed using median, and qualitative variables were described in terms of number and percentage of patients. We used the Student's test paired test and McNemar's test to compare variables at baseline and follow-up; and for variables with non-normal distribution, we used Wilcoxon rank-sum test, a non-parametric test. The laboratory results and renal response are compared based on the presence of proliferative lesions (PL) in the repeated RB using the Student's test, chi-square, and Fisher's exact test in case number of expected accounts was lower than 5.

The Kaplan–Meier estimator was used to estimate the probability distribution of not developing a renal flare after repeated RB in patients based on the existence of PL, and the comparison between groups was performed using the log rank test.

Statistical significance was set at the level of 0.05. Statistical analysis was performed using IBM SPSS Statistics version 19 (SPSS Inc., Armonk, N.Y., USA).

Results

Patients

Analysis was performed for 35 patients with proliferative LN; it was performed for those who received IC as induction therapy and for those where a repeated RB was performed (table 1). Table 2 summarizes the main clinical and laboratory features at the time of initial and repeated RB.

Treatment of LN

Sixteen (46%) patients received National Institutes of Health IC regimen [16], 7 (20%) received low-dose Euro-Lupus IC regimen [17], mean cumulative dose of 7.7 ± 3.6 g (range 3–13.6 g). Twelve (34.3%) patients received IC variables regimens with similar dose accumulated 8.3 ± 2.7 g (range 3–12.5 g). The overall mean cumulative dose of IC was 7.9 ± 3.3 g. Also, the number of IC doses was similar in NIH + Euro-Lupus regimens mean 8.8 (range 6–12) and in the variable IC regimens mean 8.9 (range 6–12).

Complications related to IC were reported in 22 (63%) patients; 10 of them (29%) presented urinary tract infections, 8 (23%) amenorrhea, 7 (20%) leukopenia, 4 (11%) herpes zoster, 1 (3%) toxic hepatitis, and 1 (3%) pancytopenia. However, these complications were not associated with the accumulated IC dose ($p = 0.21$) or age of the patients ($p = 0.51$).

Regarding corticosteroids all patients received oral prednisone, with an initial mean dose of 56 mg/day (range 50–70 mg/day), tapering according to clinical response until 10.25 ± 13 mg/day as dose of maintenance at the time of repeated RB. The cumulative dose of prednisone between the initial RB and the repeated RB was 11 ± 4 g/day/number of days. At the start of the treatment, intravenous high-doses of methylprednisolone (2.8 ± 0.4 g) were used in 16 (46%) patients due to cellular crescents. In addition,

Table 2. Clinical and laboratory features of the 35 patients with LN at the time of initial and repeated RB

	Initial RB	Repeated RB	p value
Arterial hypertension	21 (60)	19 (54)	ns
Serum creatinine, mg/dl	1.23±1.08	0.96±0.45	0.034
MDRD <60 ml/min/1.73 m ²	12 (34.3)	5 (14.3)	0.092
Proteinuria, mg/24 h	4,114.74±2,896.84	623.8±1,136.85	<0.005
Haematuria	28 (80)	7 (20)	<0.005
Nephrotic syndrome	20 (57.1)	1 (2.9)	<0.005
Anti-dsDNA antibodies, UI/ml	165.05±60.71	57.74±56.52	<0.005
CH50, U/ml	22.03±15.1	46.29±15.72	<0.005
Low C3	34 (97.1)	11 (31.2)	<0.005
Low C4	29 (82.9)	8 (22.9)	<0.005
Antiphospholipid antibodies	16 (45.7)	8 (22.9)	0.021

Values of categorical variables are the number and percentage of patients for whom continuous variables are presented as mean ± SD.

ns = Not significant.

27 (77%) patients received antimalarial drugs at the time of initial RB.

Twenty-one patients received only IC as immunosuppressive therapy. After IC, 14 (40%) patients were under the immunosuppressive maintenance treatment; of them 6 were treated with azathioprine, 6 with MMF, and 2 patients with both. The mean number of IC pulses was 9 (range 6–12).

Histological Features

Table 3 describes the histological characteristics in the initial RB and in the repeated RB. At least 10 glomeruli were available in 82% of patients in the initial RB and in the 46% of patients in the repeated RB. Of note, 26 (74.3%) patients presented non-PL (NPL) in the repeated RB, whereas 9 (25.7%) did it. Five of them (14.3%) showed ISN class III A/C and 4 (11.4%) patients showed ISN class IV A/C.

Laboratory findings at the time of repeated RB are collected in table 4 based on the presence of PL or NPL. Patients with PL presented with higher levels of 24 h proteinuria ($1,667 \pm 1,919$ vs. 262 ± 229 mg; $p = 0.001$) and lower levels of C4 (0.14 ± 0.09 vs. 0.30 ± 0.17 g/l; $p = 0.003$). Furthermore, all patients with NPL were clinical responders; 20 (77%) of them achieved a CR and 6 (23%) a partial response. One out of 9 (11%) patients with PL was in complete remission, 5 (55%) patients were in partial remission and 3 (33%) patients sustained no response. There were no differences in the induction treatment between the group with proliferative and NPL, and the time interval between initial treatment and second RB was

similar in both groups ($p = 0.7$). In PL, the mean time was 30.5 months (range 13–56), and in NPL, it was 27.4 months (range 13–40).

Therapeutic Decisions after Repeated RB

At the time of repeated RB, 21 (60%) patients developed CR, 11 (31%) patients developed partial response and 3 (9%) patients were non-responders. All patients who developed CR showed NPL, but 5 out of 11 patients who developed partial response showed PL in the repeated RB.

As far as treatment modalities are concerned, all patients were undergoing treatment with prednisone at the time of the repeated RB. Twelve patients (34%) who received oral prednisone alone of maintenance continued the same. Just after the repeated RB, 6 (17%) patients remained with the same complementary immunosuppressive therapy, 5 (14%) decreased its frequency or stopped it, and 12 (34%) increased or started a new IST; in 3 out of these patients the indication was because of extra renal SLE activity.

Long-Term Follow-Up Based on the Results of Repeated RB

Seven out of 9 (78%) patients with PL and 9 out of 26 (34.5%) patients with NPL in the repeated RB developed renal flare throughout the follow-up. Of note, the probability of renal flare throughout the first 2 years after the repeated RB was similar in both groups. However, after 48 months, the probability of renal flare-free was much lower in the group with PL than in the group with NPL, 0.375 vs. 0.799, respectively (fig. 1).

Table 3. Histological features of the study population at the time of the initial and repeated RB

	Initial RB	Repeated RB	p value
Number of glomeruli	13±6.35	9.7±4.65	0.027
ISN class: III and IV; A or A/C	33 (94.3)	8 (22.9)	<0.005
ISN 3 A/C + V		1 (2.9)	
ISN IV A + V	2 (5.7)		
No LN		2 (5.7)	
ISN class: I		1 (2.9)	
ISN class: II		11 (31.4)	
ISN IIIC		8 (22.9)	
ISN IVC		3 (8.6)	
ISN VI		1 (2.9)	
Activity index	9.94±3.39	1.32±1.96	<0.005
Chronicity index	1.57±1.61	2.47±1.79	0.001
NGEP/NG	0.18±0.185	0.032±0.019	<0.005
NGFEP/NG	0.032±0.09	0.045±0.13	0.94
NGS >80%/NG	0.04±0.086	0.18±0.15	<0.005
Interstitial leukocyte infiltration (1 + 2)*	17 (48.6)	6 (17.6)	0.001
Interstitial fibrosis (1 + 2)**	22 (62.9)	22 (62.9)	1
Tubular atrophy (1 + 2)**	17 (48.6)	17 (48.6)	1
Nephroangiosclerosis (1)**	5 (14.3)	5 (14.3)	1
Thrombotic microangiopathy	0	2 (5.7)	>0.05
Chronic injury of aPLN	1 (2.9)	1 (2.9)	1

Values of categorical variables are the number and percentage of patients for whom continuous variables are presented as mean ± SD.

* Interstitial cellular infiltration assessed as 1+: mild and 2++: moderate.

** Tubular atrophy, interstitial fibrosis and nephroangiosclerosis assessed as 1+: less than 25% and 2++: lesion between 25 and 50% of tubuli, interstitium or vessels.

A = Active lesions or A/C = active/chronic lesions in class III and IV LN according to the ISN classification; NGEP/NG = number of glomeruli with extracapillary proliferation/number of glomeruli; NGFEP/NG = number of glomeruli with fibrous extracapillary proliferation/number of glomeruli; NGS >80%/NG = number of glomeruli with glomerulosclerosis >80%/number of glomeruli; aPLN = antiphospholipid antibodies associated nephropathy.

Table 4. Laboratory and renal response according the presence of proliferative lesions and chronicity index in the repeated RB

	NPL (n = 26)	PL (n = 9)	p value
Creatinine, mg/dl	0.85±0.232	1.29±0.74	0.1
Proteinuria, g/24 h	262.7±229	1,667±1,918	0.001
C3, g/l	1.07±0.33	0.78±0.38	0.067
C4, g/l	0.3±0.17	0.14±0.09	0.003
Anti-dsDNA antibodies, UI/ml	41.76±36.8	104.11±77.93	0.056
CR	20 (77)	1 (11)	0.0009
Partial response	6 (23)	5 (55)	0.1
Non response	0	3 (33)	0.05
Chronicity index	3±2.44	2.19±1.55	0.316

Values of categorical variables are the number and percentage of patients for whom continuous variables are presented as mean ± SD.

Fig. 1. Probability of not presenting a renal flare after the repeated RB.

In other words, the median time risk over the time of renal flare after repeated RB was 45 months in patients with PL compared with 120 months in those without PL ($p = 0.046$).

At the end of follow-up, 7 out of 9 (78%) patients with PL and 4 out of 26 (15%) patients with NPL developed glomerular filtration, calculated by MDRD, <60 ml/min/1.73 m² ($p = 0.0013$). In our series, the degree of chronic lesions (glomerulosclerosis, interstitial fibrosis, tubular atrophy) in the repeated RB is not significantly associated with the deterioration of renal function at end of follow-up. Finally, 2 patients in the PL group died due to heart failure in one case and pulmonary bleeding in another case.

Adverse Events Related to RB Performance

Only 1 (3%) patient presented a severe adverse event in the form of hematoma in the lower pole, self-limited with stable hemoglobin related to the repeated RB.

Discussion

This is a retrospective study on repeated RB in 35 patients after induction therapy with IC. Unlike other studies that included patients with NPL and the induction

treatment varied, a strong point in this study is that all patients initially presented PL (III-IV A or A/C) and all received similarly induction treatment with IC. A limitation of our study is that the decision and the time to perform a repeated biopsy were based on clinical judgment and not on an established protocol. In general, the decision to perform a second biopsy was to evaluate the histological status prior to a possible therapeutic change. But the time interval between initial treatment and second RB was no different in the PL and NPL groups ($p = 0.7$).

Proteinuria is a common marker of LN activity, and the early reductions in proteinuria have been shown to be important for long-term renal outcomes in LN. The long-term follow-up of the Euro-Lupus Nephritis trial [18] and MAINTAIN trial [19] also notes that reduction in proteinuria is the most significant predictor of good response. After 12 months of treatment, the achievement of proteinuria <0.7 g/day best predicted good renal outcome, while the sensitivity and specificity were 71 and 75%, respectively [20]. In spite of this, chronic established lesions or change in ISN class V of LN can explain the reason for persisting elevated proteinuria.

In accordance with these data, higher proteinuria in the PL group versus the NPL group ($p = 0.001$) were detected at the moment of repeated RB. Interestingly, 3 of 9 patients with PL had proteinuria less than 300 mg/day.

The response criteria in the ACR [4] KDIGO [7] guidelines and European consensus [21] are defined by the decrease in urinary protein, normal or stable renal function and inactive urinary sediment. However, the discrepancy between biopsy results and clinical markers was noted and experts agreed that biopsy was the 'gold standard' for assessing renal activity and felt that more accurate biomarkers than proteinuria were needed for routine management. Repeat RB is helpful to distinguish active LN from chronic damage, in which proteinuria and rising serum creatinine may be present. However, in our series, the presence of chronic lesions (glomerulosclerosis, interstitial fibrosis, tubular atrophy) in the repeated RB is not significantly associated with elevated proteinuria.

As shown by other studies [8, 9, 22, 23], we found persistent histopathological renal activity despite apparent clinical response. Furthermore, PL in repeated RB was associated with more frequent and early risk of renal flare.

The definition of response to treatment based on clinical criteria may affect the results of trials of new treatment methods. A large number of uncontrolled studies [24–27] have suggested the efficacy of rituximab in LN, but it did not improve clinical outcomes in one randomized clinical trial. LUNAR trial [28] was a double-blind,

placebo-controlled phase III study recruiting patients with active PL LN (class III or IV), which aimed at assessing the efficacy and safety of rituximab in patients treated with mycophenolate mofetil and corticosteroids. The results demonstrated non-significant improvement in the rituximab-treated group, based on the proportion of patients achieving a CR, defined by low levels of proteinuria, a normal serum creatinine level, and negative urine sediment. However, 15% of patients showed partial response in this group. Limiting the approach to clinical response may be a problem in clinical trials and this could lead to study failure. For this reason, it has been suggested that the realization of the repeated RB should be considered in the study design of future clinical trials [29].

Effective induction therapy is also expected in the reduction of serologic markers of lupus activity. The reported sensitivity and specificity of anti-dsDNA antibodies and low levels of complement appear as 77 and 73%, respectively [7]. In our patients, the levels of anti-dsDNA were greater in the PL group than in the NPL group in the repeated RB but not statistically significant. Complement levels were also lower in the PL group than in the NPL group, but only low levels of C4 were statistically significant.

New biomarker development for LN is still in an early stage and the majority of studies have focused on identifying biomarkers that reflect disease activity. But if the disease activity is defined by standard methods, such as proteinuria, urine sediment, and serum creatinine, the novel biomarkers can be no better than these measurements [30]. To improve on standard methods, novel biomarkers must be judged against an activity measurement that is superior such as the kidney biopsy [22].

In our study, just after repeated RB, 14% ($n = 5$) of patients decreased or stopped IST, and 34% ($n = 12$) increased or started a new IST, 6 of them showed proteinuria less than 1 g/day, and in 3 of these patients, the indication was because of extra renal SLE activity. In 20 out of 32 patients, repeated RB was crucial to adjust the treatment. The discordance between histopathological findings and the laboratory variables routinely used to define disease activity, and also the prognostic information obtained from repeat renal biopsies, emphasize that it is important to evaluate clinical response and adjust treatment in LN.

While the RB after diagnosis is a well-established practice in suspected relapse, the use of this practice in CR or partial response situations is a matter of debate. An RB is an invasive procedure with associated morbidity, that can be performed only if all or patients with certain features should be biopsied. The questions of who should undergo

biopsy and when still remain and finally histological response criteria have not been established.

A repeated RB can be a valuable tool, particularly in patients under partial response, to distinguish patients in true remission from those in apparent remission. This helps in identifying patients who could benefit from intensified treatment, avoiding future irreversible damage, and avoiding unnecessary aggressive treatments when irreversible renal damage is found.

Although the small number of patients included and the retrospective nature of this and other studies in the literature [8, 9] make it difficult to arrive at definitive conclusions about the usefulness of the RB in monitoring the response in LN, these data insinuate their utility. Future prospective studies are needed.

Key Messages

RB after induction in LN class IV and III distinguishes true from apparent remission.

Repeated RB provides additional understanding; adjust treatment plans to avoid irreversible renal damage or unnecessary aggression.

Repeated RB provides predictive usefulness regarding the risk time of renal flare and guide treatment.

Contributors

P.A. and G.E.: study design, construction of the database with clinical information and interpretation of results. M.S.: assessment of all the initial and repeated renal biopsies. G.J.P. and R.M.A.: statistical analyses, interpretation of results and manuscript writing. All authors made substantial contribution to the following: drafting the article or revising it critically for important intellectual content; final approval of the version published.

Disclosure Statement

The authors declare no conflicts of interest.

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