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Original Article

ORIGINAL ARTICLE

Kidney biopsy in lupus nephritis after achieving clinical renal remission: paving the way for renal outcome assessment

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ABSTRACT

The role of repeat kidney biopsy in lupus nephritis (LN) with renal remission is unclear. The aim of this study was to assess this role in a real-life scenario. This retrospective, single-centre study included 56 patients with LN diagnosed from 1998 to 2019, with an initial kidney biopsy (KB1) at the onset of LN and a second kidney biopsy (KB2) after achieving renal remission. A total of 51 (91.1%) patients were women with a median age of 29.9 years [interquartile range (IQR) 23.4–40.6] at the time of LN diagnosis. KB2s were performed after 41.1 months (IQR 30.1–52.5) of KB1. At the time of KB2, complete renal response was achieved in 51 (91.1%) patients. The median activity index decreased from a baseline value of 6.5 (IQR 2.8–11) to 0 (IQR 0–2) ($P < .001$). The chronicity index worsened from 1 (IQR 0–2) to 2 (IQR 1–3) ($P = .01$). In patients with proliferative/mixed forms at KB2, the chronicity index median value increased to 3 (IQR 1.5–4), as well as interstitial fibrosis and tubular atrophy ≥25%, from 5.4% to 13.5%. Persistent histological active LN (activity index ≥2) was present in 11 (19.6%) KB2s. There were no differences when comparing immunological parameters between both groups (activity index ≥2 versus <2) at KB2, nor in the percentage of patients who presented renal flare. Immunosuppressive treatment was withdrawn in 35 (62.5%) patients and maintained/switched in 21 (37.5%). Afterward, new renal flare occurred in 9 patients per group (25.7% and 43%, respectively), after a median time of 39 months (IQR 6.5–55) and 7 months (IQR 6–30), respectively. There was no difference in the number of patients who developed chronic kidney

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disease [$n = 14$ (25%)] according to the treatment. In conclusion, KB2 provides valuable information to guide immunosuppressive maintenance therapy.

Keywords: chronic kidney disease, clinical remission, lupus nephritis, repeat biopsy

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a relapsing–remitting course. Its pathogenesis involves genetic, immunoregulatory, hormonal and environmental factors [1]. Lupus nephritis (LN) is the most important predictor of morbidity and mortality and may be present in almost 30% at the onset of disease and up to 50–60% during the first 10 years of the disease [2]. In fact, the Euro-Lupus Nephritis Trial cohort demonstrated that LN is a relevant survival prognostic factor at 10 years [3]. Kidney biopsy not only permits LN confirmation, but can also provide prognostic value and is currently still considered the gold standard for diagnosis [4].

Treatment goals for newly diagnosed LN patients include achieving remission by induction therapy followed by maintenance treatment for at least 3 years to avoid renal flares and prevent chronic damage [5]. Overall, the renal response rate approaches 50% at 6 months and may reach 65–80% at 12–24 months of treatment [6]. Although the role of a renal biopsy at the first presentation of kidney involvement in lupus is well established, the role of a repeat biopsy is less clear. Nowadays, repeat biopsy is considered in selected cases, such as worsening of renal outcomes, non-responsiveness to immunosuppressive treatment or at relapse to demonstrate possible histologic class transition or a change in the chronicity and activity index. Also, some scientific societies recommend a repeat biopsy when there is therapeutic uncertainty in the follow-up for the evaluation of signs of activity and chronicity of the disease [1]. However, the role of protocol repeat biopsies in patients with a complete or partial clinical response is controversial. On the one hand, the latest update of the European League Against Rheumatism (EULAR) recommendations for the management of LN only suggests the gradual withdrawal of treatment in patients in complete renal response (CRR) after 3–5 years of treatment but does not include a new biopsy to guide this decision. On the other hand, protocol repeat biopsies have shown considerable discrepancies between clinical and histological findings [7]. Data from observational studies [8–12] suggest that a repeat biopsy may help guide the decision to intensify, withdraw or maintain immunosuppression therapy. In fact, Alsuwaida *et al.* [13] found that even a low activity index (AI) of 1 or 2 at the second kidney biopsy could be associated with a higher risk of poor renal outcome whereas the chronicity index was similar regardless of renal response status. In another study, AI scores >2 on repeat biopsies were associated with renal relapses {odds ratio [OR] 6.2 [95% confidence interval (CI) 1.2–33.8]; $P = .035$} and a shorter time to relapse [hazard ratio (HR) 1.2 (95% CI 1.1–1.3); $P = .007$] [11].

Thus, the aim of the present study was to assess, in real life, the role of repeat kidney biopsies in patients with LN, CRR or partial renal response (PRR).

MATERIALS AND METHODS

Study design

This retrospective, single-centre study included 56 adult (defined as ≥18 years old) patients with a diagnosis of SLE according to the 1982 revised American College of Rheumatology SLE classification criteria [14] and biopsy-proven LN according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification [15], who were jointly followed up at the Department of Autoimmune Diseases and the Department of Nephrology and Kidney Transplantation, Hospital Clinic, Barcelona, Spain, from January 1998 to March 2019. All selected patients had an initial kidney biopsy at the onset of LN and a second kidney biopsy after achieving renal remission. The induction and maintenance treatment regimens were based on the EULAR recommendations and the decision to carry out the second biopsy was agreed jointly by the treating physicians following the centre's clinical guidelines. The study was approved by the Clinical Research Ethics Committee of the Hospital Clinic of Barcelona (HCB/2018/1221).

Clinical and laboratory variables

The following variables were retrieved from the medical records of the patients: demographic variables (gender, ethnicity, age at SLE diagnosis and renal involvement), smoking, concomitant clinical variables related to LN that included arterial hypertension and renal function parameters such as serum creatinine, estimated glomerular filtration rate (eGFR); calculated using the Modification of Diet in Renal Disease study equation) [16], 24-h urine protein (g/24 h) and haematuria (≥5 red blood cells/field) or urine cast. Furthermore, immunological parameters were also considered, including serum levels of anti double–stranded DNA (dsDNA) antibodies, complement 3 and 4 (C3 and C4) and antiphospholipid (aPL) antibodies, namely lupus anticoagulant (LA) and immunoglobulin G/M (IgG/IgM) isotypes of anticardiolipin (aCL) antibodies and anti-β2-glycoprotein I (aβ2GPI) antibodies. The activity of SLE was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K) [17]. All these variables were collected at the two time points of the study (at the time of the first and second kidney biopsy). Induction and maintenance treatment and gestational desire were also included in the analysis.

Renal pathology evaluation

Baseline and repeat biopsies were evaluated by two experienced nephropathologists, processed with light and immunofluorescence microscopy and classified using the 2003 ISN/RPS classification of LN [7]. Biopsy samples were processed using haematoxylin and eosin, periodic acid–Schiff, Masson's trichome and methenamine-silver staining; immunofluorescence reports scored intensity on a 0–3+ scale. Renal activity and chronic damage were determined using the National Institutes of Health (NIH) AI and chronicity index, respectively [18]. An AI ≥2 was considered a marker of significant activity according to the study of Alsawaida *et al.* [13]. Interstitial fibrosis (IF) and tubular atrophy (TA) defined as the IFTA score (absence of IFTA lesions in renal biopsy = 0, <25% = 1, 25–50% = 2, >50% = 3) [19] and the presence of thrombotic microangiopathy in the context of aPL antibodies were taken into account. Biopsy procedure complications, such as severe haematoma that required blood product transfusion, radiologic interventionism or vasoactive drugs, were reported.

Definition of renal response and flare

We used the definitions of CRR, PRR and renal flare proposed by the EULAR and European Renal Association–European Dialysis and Transplant Association [6]. Follow-up was defined as the time from the first to the second kidney biopsy and subsequently, until the last outpatient appointment. Advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) according to the definition of the Kidney Disease: Improving Global Outcomes guidelines [20] or the need for dialysis and/or renal transplant and death were also recorded.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 21 (IBM, Armonk, NY, USA). Qualitative variables were described as percentages and quantitative variables as mean ± standard deviation (SD) or median [interquartile range (IQR)] in the case of extreme values. In the case of categorical variables, we used the chi-squared and Fisher's exact tests to establish differences between groups. In the case of quantitative parameters, we used different tests depending on the analysis. The McNemar test and the Wilcoxon signed rank test were used to examine differences within the same group (AI <2 or AI ≥2) before and after treatment and the Mann–Whitney test was used to examine differences between both study groups (AI <2 versus AI ≥2) after treatment. The unavailable data were declared as missing values. Bivariate and multivariate analysis was performed to identify predictors of LN flare after adjusting immunosuppression or ESRD development and were expressed as OR (95% CI). To investigate the effect of several variables on the time required for both events to happen we used a Cox regression. *P*-values ≤.05 were considered statistically significant.

RESULTS

General characteristics

A total of 56 adult patients were included with a median follow-up of 150.8 months (IQR 101.9–218.9) from the diagnosis of SLE. Demographic, clinical characteristics, laboratory features and histological findings at baseline (at LN diagnosis) are described in Supplementary data Table S1. In the whole series, 51 (91.1%) patients were women with a median age of 27.6 years (IQR 19.4–35) at the time of SLE diagnosis and 29.9 years (IQR 23.4–40.6) at the time of LN diagnosis. Considering extrarenal involvement at baseline, mucocutaneous manifestations were the most frequent, present in 43 (76.8%) patients, followed by lymphopaenia in 42 (75%), arthritis in 29 (51.8%), serositis in 8 (14.3%) and thrombocytopaenia in 7 (12.5%).

In all, 42 (75%) episodes of LN corresponded to naïve LN flare and in 28 (50%) episodes it was the presenting manifestation of SLE. Of note, the reason for repeating the renal biopsy was to guide the immunosuppressive maintenance therapy (to maintain or discontinue it gradually) and, more specifically, in 7 (12.5%) women prior to a future pregnancy (gestational desire). Patients were followed for a median of 125.1 months (IQR 79.1–187.3) from LN and 66.8 months (IQR 12.9–99.5) from the repeat biopsy to the last control.

SLEDAI, laboratory features and treatments at baseline and repeat biopsy

At the time of the repeat biopsy, immunological parameters had improved (Table 1). However, anti-dsDNA antibody levels remained elevated in 30 (54.5%) patients and hypocomplementaemia was present in 21 (37.2%). In addition, the SLEDAI decreased from a baseline median of 14 (IQR 11.3–20) to a median of 2 (IQR 0–4) ($P < .001$) at the time of repeat biopsy. Regarding renal parameters, there were no significant differences in eGFR and in the percentage of patients with IFTA < 25%, which remained stable. Haematuria persisted in eight (14.3%) patients. Induction and maintenance treatment regimens are described in Table 1. CRR at the time of repeat biopsy was achieved in 51 (91.1%) patients and PRR in 5 (8.9%) and the median time to achieve clinical remission was 9 months (IQR 4–17.5).

Renal pathology characteristics at repeat kidney biopsy and complications related to biopsy

Repeat biopsies were performed after a median time of 41.1 months (IQR 30.1–52.5) from the first renal biopsy, taking into account that in 42 patients it coincided with the debut of LN versus 14 in whom this flare appeared later because they were relapsing cases. In repeat biopsies, the pure proliferative LN class persisted in 34 of the 49 baseline pure proliferative biopsies (69.4%), whereas the membranous LN class persisted in four of the five baseline biopsies (80%). Overall, histological transition was evidenced in 15 (26.8%) cases (Table 2).

In addition, the median AI decreased from a baseline value of 6.5 (IQR 2.8–11) to 0 (IQR 0–2) ($P < 0.001$) at the time of the repeat biopsy. Conversely, the chronicity index worsened from 1 (IQR 0–2) to 2 (IQR 1–3) ($P = 0.01$) (Table 1). In those patients with proliferative/mixed LN at repeat biopsy, an AI >0 persisted in 14 (37.8%) patients, with a median AI of 0 (IQR 0–2) and the median chronicity index increased to 3 (IQR 1.5–4), as well as IFTA ≥25%, from 5.4% to 13.5%. Thrombotic microangiopathy was demonstrated in one patient with aPL triple positivity.

The rate of procedure-related complications was low. In all, seven (12.5%) patients suffered from self-limited renal haematoma and only one (1.8%) of them required a blood transfusion.

Relationship between immunological and renal pathology features at repeat biopsy

We aimed to study if the levels of anti-dsDNA antibodies, C3 and C4 correlated with the AI on repeat biopsy. For this purpose, we considered persistent histologically active LN with an AI ≥2 (Supplementary data, Table S2). Overall, it was presented in 11 (19.6%) repeat biopsies, which accounted for one-third of the proliferative and mixed classes (29.7%). Compared with those at the onset of LN, the immunological parameters (anti-dsDNA antibodies and complement) improved in both groups at the time of the second biopsy. However, the differences were only statistically significant in the group with AI <2. There were no differences when comparing immunological parameters between both groups (AI ≥2 versus AI <2) at the moment of repeat biopsy.

Treatments after repeating renal biopsy and follow-up

Follow-up according to the histological remission (AI <2) and treatment after repeating renal biopsy are described in Table 3 and Fig. 1. According to the results of the second biopsy and to the criteria of the treating physicians, immunosuppressive treatment was gradually withdrawn in 35 (62.5%) patients, maintained in 16 (28.5%) and intensified/switched in 5 (8.9%) based on histological activity in 3 cases and desire for pregnancy in 2,

Table 1. SLEDAI, laboratory and immunological features, histological findings and treatments at baseline (LN diagnosis) and repeat biopsy

	Baseline	Repeat biopsy	P-value
SLEDAI, median (IQR)	14 (11.3–20)	2 (0–4)	<.001
Laboratory features, median (IQR)			
Serum creatinine (mg/dL)	0.9 (0.7–1.2)	0.8 (0.7–0.9)	.5
eGFR (mL/min/1.73 m^2)	68 (53.5–90)	80 (60–90)	.3
24-h proteinuria (mg/24 h)	2871 (1280–4902)	136 (81–202)	<.001
Haematuria, *n* (%)	41 (73.2)	8 (14.3)	.001
Immunological parameters, median (IQR)			
Anti-dsDNA antibodies (UI)[a]	178 (100–200)	28 (13–95.1)	<.001
C3 (g/L)[b]	0.6 (0.3–0.7)	0.9 (0.7–1.1)	<.01
C4 (g/L)[c]	0.07 (0.07–0.12)	0.2 (0.1–0.2)	.001
Histological findings, median (IQR)			
Activity index	6.5 (2.8–11)	0 (0–1)	<.001
Chronicity index	1 (0–2)	2 (1–3)	.01
IFTA score <25%, *n* (%)	43 (76.8)	46 (82.1)	.7
Treatments, *n* (%)	As induction phase[d]	As maintenance phase	
Corticosteroids	54 (96.4)	51 (91.1)	
Prednisone dose (mg/day), median (IQR)	50 (30–60)	5 (2.5–5)	
Cyclophosphamide	33 (58.9)	5 (8.9)	
Mycophenolate	24 (42.9)	33 (58.9)	
Rituximab	4 (7.1)	0	
Obinutuzumab	1 (1.8)	0	
Mycophenolate + Tacrolimus	1 (1.8)	0	
Tacrolimus	0	3 (5.4)	
Azathioprine	0	15 (26.8)	
Antimalarials	45 (80.4)	48 (84.2)	
ARA or ACE inhibitors	31 (55.4)	44 (60.7)	

[a]Normal range <20.00 UI.
[b]Normal range 0.870–1.700 g/L.
[c]Normal range 0.110–0.540 g/L.
[d]Six patients required induction therapy readjustment due to refractoriness: two switched from cyclophosphamide to mycophenolate and rituximab, two added rituximab to mycophenolate, one added tacrolimus to mycophenolate and one was included in a clinical trial assessing the role of obinutuzumab added to mycophenolate.
ACE, angiotensin-converting enzyme; ARA, angiotensin receptor antagonist.

Table 2. Transitions in LN classification (ISN/RPS 2003) from the first to the second biopsy

LN class at first (baseline) biopsy, (*N* = 56)	LN class at second biopsy (*n* = 56)[a]								
	II	III	IV	V	Mixed	VI	Indeterminate	Normal histology[c]	Transition[b], *n* (%)
II (*n* = 1)	**1**	0	0	0	0	0	0	0	0
III (*n* = 13)[a,c]	2	**6**	2	0	0	0	1[a]	2	4 (7.1)
IV (*n* = 36)[c]	4	16	**10**	2	1	1	0	2	10 (17.9)
V (*n* = 5)	0	0	0	**4**	1	0	0	0	1 (1.8)
Mixed (*n* = 1)	0	0	0	0	**1**	0	0	0	0
Total[c]	7	22	12	6	3	1	1	4	15 (26.8)

[a]The histological class of LN at the second biopsy could not be accurately determined in one patient with class III at baseline biopsy.
[b]Transition from non-proliferative (class II) to proliferative (class III or IV) or membranous (class V) or mixed, transition from proliferative (class III or IV) to non-proliferative (class II) or membranous (class V) or mixed and transition from membranous (class V) to non-proliferative (class II) or proliferative (class III or IV) or mixed.
[c]The renal histology was normal in the second biopsy in four patients (two with class III and two with class IV at the first biopsy).
The numbers in bold represent the number of biopsies that maintain the same histological class.

respectively. Since adjustment therapy, 18 (32.1%) patients presented a new renal flare and 14 (25%) developed CKD (10 patients stage 2, 4 patients stage 3 and none ESRD).

In the group of patients in whom immunosuppression was maintained or switched, women expressing gestational desire were overrepresented (29% versus 3%; *P* = .009), more patients presented with high levels of anti-dsDNA antibodies (71.4% versus 42.9%; *P* = .02) and the median levels of anti-dsDNA antibodies were higher [18.5 (IQR 9.2–51.2) versus 45 (28–117); *P* = 0.03)]. During follow-up, a new renal flare occurred in nine (25.7%) patients in whom immunosuppression was withdrawn, after a median time of 39 months (IQR 6.5–55), whereas a new renal flare occurred in nine (43%) patients in whom immunosuppression was maintained or switched, after a median time

Table 3. Comparative analysis of clinical characteristics, histological features and immunological parameters after repeat kidney biopsy

	Immunosuppression withdrawal ($n = 35$)	Immunosuppression maintenance/switching ($n = 21$)	P-value
Complete renal response, *n* (%)	32 (91.4)	19 (90.5)	.9
Gestational desire, *n* (%)	1 (2.9)	6 (28.6)	.009
Naïve LN, *n* (%)	30 (85.7)	12 (57.1)	.02
LN class III–IV at repeat biopsy, *n* (%)	24 (68.6)	13 (61.9)	.41
Activity index ≥2 at repeat biopsy, *n* (%)	4 (11.4)	7 (33.3)	.03
Anti-dsDNA antibodies at repeat biopsy, *n* (%)	15 (42.9)	15 (71.4)	.02
Anti-dsDNA levels titre (UI), median (IQR)	18.5 (9.2–51.2)	45 (28–117)	.03
Complement at repeat biopsy			
Low complement, *n* (%)	12 (34.7)	9 (42.9)	.34
C3 level (g/L), median (IQR)	0.9 (0.8–1.1)	0.8 (0.6–1.1)	.79
C4 level (g/L), median (IQR)	0.2 (0.1–0.2)	0.2 (0.1–0.2)	.12
24-h proteinuria (mg) at repeat biopsy, median (IQR)	117 (76–202)	152 (111–239.8)	.37
Follow-up (months), median (IQR)	119.8 (76.1–172.8)	126.4 (99.5–199.6)	.78
Events during follow-up			
Renal flare, *n* (%)	9 (25.7)	9 (42.9)	.06
Time to renal flare (months), median (IQR)	39 (6.5–55)	7 (6–30)	.07
Chronic kidney disease, *n* (%)	8 (22.9)	6 (28.6)	.43
Stage II	5 (14.3)	5 (23.8)	1
Stage IIIA	2 (5.7)	1 (4.8)	.64
Stage IIIB	1 (2.9)	0 (–)	–

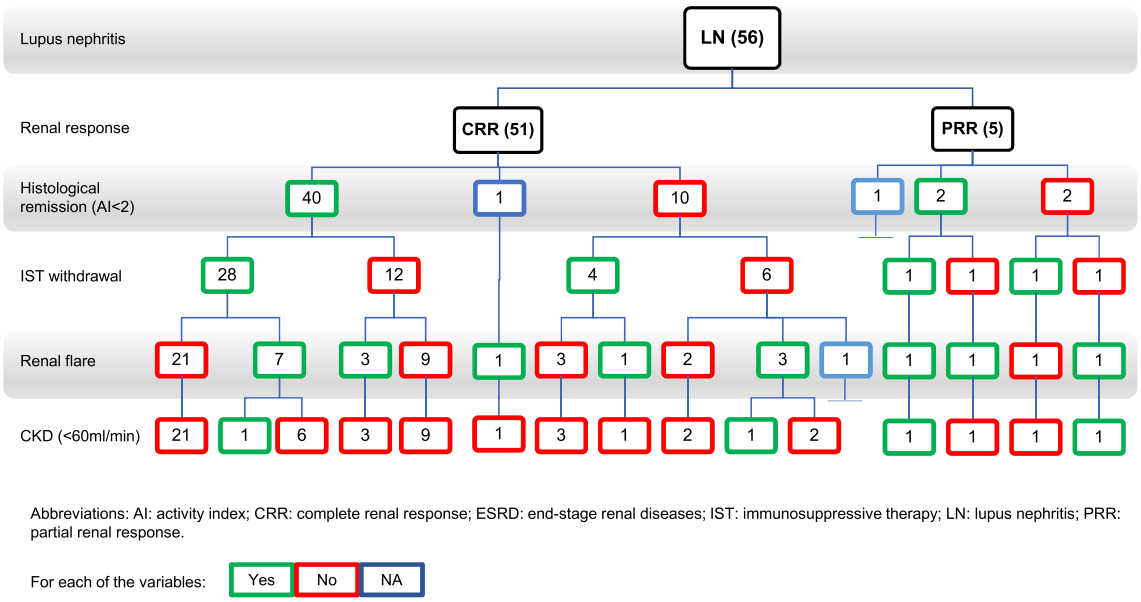

FIGURE 1: Follow-up flowchart. Rate of flares and ESRD according to the type of clinical remission and therapy.

of 7 months (IQR 6–30) (Table 3). There was no difference in the number of patients who developed CKD (mild, moderate or severe) during follow-up according to the treatment. In the overall series, no patient required haemodialysis or died during follow-up.

There were no differences in the percentage of patients who presented renal flare according to the AI in the repeat renal biopsy (36.4% in AI ≥2 versus 30.2% in AI <2; $P = .12$) nor was any relationship found with the treatment received after the second biopsy.

New renal flares after remission and evolution to ESRD

These two outcomes were analysed independently. First, regarding new flares, male gender, PRR and an absence of concomitant antimalarial treatment were related to recurrence of LN, but only the absence of antimalarial therapy demonstrated an increased risk in multivariate analysis [OR 21.7 (95% CI 1.4–41.4); $P = .04$] (Table 4). Although the relationship with AI was not significant, patients with a higher index had an earlier relapse compared with those with AI <2 (Table 4).

Table 4. Risk of new flare during follow-up after second renal biopsy and treatment strategy

	Bivariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Gender (male)	6.19 (2.53–10.28)	.01	1.9 (0.7–6.53)	.9
No smoking	0.41 (0.11–2.34)	.52	–	–
Age at SLE diagnosis	0.03 (0.01–1.51)	.87	–	–
Age at LN diagnosis	0.05 (0.02–2.75)	.83	–	–
Naïve (first kidney flare)	0.41 (0.21–1.63)	.52	–	–
Proliferative LN (at baseline)	0.09 (0.02–2.45)	.77	–	–
Time to remission	0.001 (0.0002–3.89)	.98	–	–
PRR (versus CRR)	6.19 (2.23–10.56)	.01	1.8 (0.17–4.98)	.9
Proliferative LN (at repeat biopsy)	3.07 (0.89–5.78)	.15	–	–
AI ≥2	1.43 (0.77–4.29)	.23	–	–
Anti-dsDNA (negative)	0.48 (0.22–2.13)	.49	–	–
Complement (normal)	0.27 (0.03–4.79)	.60	–	–
IS maintenance/switched	0.89 (0.17–3.65)	.34	–	–
No concomitant antimalarial	3.45 (1.32–5.73)	.03	21.7 (1.4–41.4)	.04

IS, immunosuppressive treatment.

Table 5. Risk of ESRD during follow-up

	Bivariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Gender (male)	0.05 (0.02–2.71)	.82	–	–
Non-smoking	0.26 (0.03–1.92)	.61	–	–
Age at SLE diagnosis	3.58 (0.84–6.87)	.058	–	–
Age at LN diagnosis	7.46 (1.71–14.59)	.006	1.42 (1.08–1.74)	.04
Naïve (first kidney flare)	0.035 (0.01–1.42)	.85	–	–
Time to remission	0.75 (0.06–6.91)	.39	–	–
PRR	2.44 (0.83–5.67)	.12	–	–
Proliferative LN	0.04 (0.02–1.72)	.84	–	–
Chronicity index	6.89 (2.37–11.13)	.009	2.39 (0.46–7.27)	.26
IFTA ≥25%	3.69 (0.93–7.34)	.055	–	–
IS maintenance/switched	0.47 (0.02–3.93)	.49	–	–
New flare after IS adjustment	1.68 (0.35–7.89)	.19	–	–

IS, immunosuppressive treatment.

Second, regarding the evolution to ESRD, older age at LN diagnosis was related to CKD in both the bivariate and multivariate analysis [OR 1.4 (95% CI (1.08–1.74); $P = .04$]. A higher chronicity index showed a relevant trend but was not significant in multivariate analysis (Table 5).

DISCUSSION

In this retrospective study we analysed the role of repeat biopsies in LN patients with CRR or PRR. Few studies have examined protocolized repeat kidney biopsies in LN and these were mostly focussed on correlating the inflammatory activity present in the biopsy with the risk of developing a renal flare. In this sense, Parodis *et al.* [11] found that high AI scores in repeat biopsies were associated with an increased probability and/or shorter time to renal relapse following repeat biopsy, independent of proteinuria levels. Malvar *et al.* [10] went a step further, designing a prospective observational study where the management of LN was based on kidney histology determined by biopsies repeated at prespecified intervals. In that study, the cohort ($n = 76$) was followed up a median of 96 months (range 53–155). Maintenance therapy in those patients was withdrawn if the biopsy showed an AI of 0 in the biopsies repeated at prespecified intervals but was continued if the biopsy showed an AI ≥1. Only seven patients (9.2%) developed an LN flare during follow-up, significantly less than reported flare rates. No patient died or developed ESRD and kidney function worsened in seven patients (four of them developing *de novo* CKD). They concluded that combining kidney histology and clinical findings may help limit immunosuppressive exposure, reduce flare rate and improve kidney and patient survival compared with LN patients managed using clinical data only.

In our cohort there were no differences in the number of patients who presented with a renal flare according to the AI in the repeat renal biopsy (36.4% in those with AI ≥2 versus 30.2% in those with AI <2; $P = .12$). Moreover, we did not find any difference when comparing immunological parameters between both groups.

Since our study was retrospective and based on real-life management, the findings in the repeat biopsy were not the only criteria followed to decide the withdrawal or the maintenance/switch of immunosuppressants. Other factors were relevant, such as gestational desire and immunological and laboratory parameters. Based on all these data, and not only

histologic data, treatment was withdrawn in 35 patients and maintained/switched in the remaining 21. Although there were no significant differences in the percentage of patients in each group who subsequently presented a renal flare (nine patients per group, which represents 25.7% and 42.9% in each group, respectively; $P = .06$), the time to renal flare in the withdrawal group tended to be longer than in the maintain/switch group [39 months (IQR 6.5–55) versus 7 (6–30); $P = .07$). These data suggest that those patients in whom, according to the biopsy findings among other criteria, immunosuppression is withdrawn, have a high negative predictive value for a renal flare in the short term. Since no significant differences were observed in any of the other parameters, except for a higher anti-dsDNA titre in the group in which immunosuppression was maintained, having histological information on these patients was especially important for guiding treatment decisions. With these data, the hypothesis is that maintaining immunosuppression according to the findings of the repeated biopsy would reduce the risk of renal flare in the short term gains value.

However, the prediction of a renal flare, in our understanding, is not the main objective when performing a repeat biopsy, but rather to evaluate the persistence of inflammation that does not manifest clinically and also to characterize the degree of chronicity and fibrosis, the main determining factors of progression to CKD.

In the study of Zickert *et al.,* [21] up to 29% of LN patients with clinical remission had active lesions on repeat biopsies, i.e. histological non-response. Malvar *et al.* [22] reported similar results (one-third of patients with clinical remission). In our series, 91.1% of the patients achieved CRR at the time of repeat biopsy, and only 8.9% of the patients presented a PRR, which carried a higher risk of relapse. On the one hand, the current data confirm the importance of not being satisfied with just getting a partial response but looking for a CRR. However, even more striking and with a greater potential impact on clinical practice was the fact that 21.4% of patients under clinical remission criteria had an AI $\geq$2 on repeat biopsy. Urinary and serological markers correlate poorly with histology and therefore there is always some uncertainty about when or if remission of LN has been achieved. In contrast, it is very common to observe patients with complete histologic remission on rebiopsy that is immunologically 'active' [22], with a low-grade proteinuria indistinguishable from that secondary to active lesions. In fact, characteristically, tubulointerstitial injury is manifested by low-grade proteinuria, which can lead to the false conclusion of disease control.

In this sense, the definition of renal flare is a matter of controversy or discussion. Currently the most used criteria are determined by the variation of proteinuria, GFR and changes in urinary sediment. In fact, the remission criteria mostly used in clinical trials, called ordinal renal response (complete, partial or refractory/no response), are based on this concept. However, the different series show that a non-negligible percentage of patients maintain a certain degree of activity in the repeat biopsy, in what we could call persistent low-grade inflammation. This persistent active inflammation of the renal parenchyma silently leads to IFTA and thus the progression of CKD. Therefore, rather than considering whether an AI $\geq$2 leads to a higher risk of renal flare, we should consider persistent renal inflammatory activity at an AI $>$ 0, similar to the design proposed in the study of Malvar *et al.* [10].

Regarding serum creatinine, it is well known that it is not a good marker to predict the histological severity (active and/or chronic) of LN. In fact, in our series there were no significant differences in eGFR at the time of the baseline and repeat biopsy. However, the chronicity index worsened from 1 (IQR 0–2) to 2 (IQR 1–3) ($P = .01$), and particularly in patients with proliferative/mixed forms, in whom the chronicity index median value increased to 3 (IQR 1.5–4), as well as IFTA $\geq$25%, from 5.4% to 13.5%. This can be explained in part by the renal reserve, which makes it possible to maintain normal creatinine values but which does not reflect the underlying kidney damage and therefore underestimates the severity and the risk of progression to CKD. This point is especially important, as these patients are generally young and will need to maintain the best possible kidney function for many years. In our series, up to 25% of the patients developed CKD. Therefore, in these patients, treatments will not only be focussed on the processes that trigger the initial damage in the kidneys, but also manage the mechanisms that engage the process of inflammation and fibrosis to avoid further damage. So far, the therapeutic alternatives in this regard have been limited and for many years angiotensin-converting enzyme inhibitors and angiotensin II antagonists have been the only option to ameliorate renal fibrosis. In recent years, new alternatives have appeared that reduce the progression of CKD, such as sodium-glucose cotransporters-2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists and, more recently, finerenone, a mineralocorticoid blocker receptor [23]. All of them deserve to be explored in order to optimize renal outcomes in LN patients.

In our experience, with an early diagnosis of LN, despite 25% of the patients presenting with CKD, none of them required renal replacement therapy or developed ESRD. Moreover, only four patients had CKD stage 4. This better renal prognosis, compared with those reported in the first series of patients with LN [24] should not be attributed only to the incorporation of repeated biopsy in the management algorithm of these patients, but also to the greater knowledge of the disease, the use of new treatments and, finally, the new tools in recent years to slow the progression of CKD, mentioned above. Moreover, we must take into account that these patients were patients who had achieved renal remission. These findings correlate with a slow progression of chronic kidney lesions and with the stability of the proportion of patients with mild IFTA during the interbiopsy period. However, early diagnosis and treatment can also be a challenge in monitoring the disease, since, in patients with low levels of proteinuria at diagnosis, the decrease in proteinuria will be smaller compared with those in the nephrotic range, hence we need other tracking tools. Thus maintenance therapy in these patients should not only include immunosuppressive treatment, but also nephroprotective treatment, guided by renal biopsy findings, and a multidisciplinary approach [25].

These data should be considered with caution, as the study has certain limitations. First, it is a retrospective study with a small number of patients. In addition, the study period includes periods of considerable change and transition in treatment guidelines, both in the treatment schedule and in the use of new drugs. Likewise, the variability in the treatment received by the patients, in many situations guided also by extrarenal symptoms and/or gestational desire, makes it difficult to analyse the results. And, finally, because of variability when performing the repeat biopsy. However, many of these limitations are in turn strengths, since they precisely reflect the day-to-day scenario of these patients, i.e. real-life situations.

In conclusion, repeated biopsy after achieving partial or complete remission provides valuable information to improve the quality of life and safety of patients with SLE in the long term, since it allows a more personalized maintenance therapy, minimizes the risk of complications during pregnancy, estab-

lishes the degree of chronicity of kidney tissue and the potential benefits and risks of future treatments in case of a new recurrence. In essence, we should probably transition from 'proteinuric' to 'histologic' criteria to define CRR. We will better justify the control biopsy when we understand that the presence of persistent low-grade inflammatory activity, whether clinically visible or not, is a factor of progression to CKD and when we understand that low-grade proteinuria may be a sign of chronicity rather than activity.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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