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Review Article

The value of repeat kidney biopsy in lupus nephritis. A systematic review

Susy Marcela Sánchez-Cubías, Guillermo Arturo Guaracha-Basañez, María Graciela Sandoval-Flores, Maricruz Domínguez-Quintana, Juanita Romero-Díaz*

Department of Immunology and Rheumatology, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico

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ABSTRACT

A renal biopsy is the 'gold standard' for diagnosis and classification of lupus nephritis (LN). The role of repeat renal biopsy in lupus nephritis (LN) to guide treatment or predict prognosis has been controversial. A systematic literature review was conducted based on retrospective and prospective studies. The studies were identified using English electronic scientific databases, including MEDLINE PUBMED, published between January 1990 and August 2020. The eligibility criteria were studies including adult LN patients with at least one follow-up renal biopsy with appropriate longitudinal information. Case reports, studies with incomplete information or including duplicate patients were excluded. Based on the inclusion and exclusion criteria, a total of 73 publications were identified. This study included a total of 1167 repeat biopsies in LN patients from 15 studies. The primary indication for a repeat biopsy was relapse in 44-78% of the cases, and lack of response in 13-51%. Additionally, several repeat biopsies were done according to the protocol, after induction and maintenance therapy. In terms of histopathological class switches, there was a higher frequency of changes from nonproliferative to proliferative lesions. Only two studies provide a definition of histological response. There were often changes in the therapeutic approach after a repeat biopsy. Repeat kidney biopsies are helpful in patients with LN flare/relapse, and in patients with poor treatment response. Histological transformation was a common finding. The histologic and clinical responses are discordant. A repeat biopsy could be of prognostic value for therapeutic decision-making.

* Corresponding author.
E-mail address: susymarces@gmail.com (S.M. Sánchez-Cubías).
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La utilidad de la biopsia renal repetida en nefritis lúpica. Una revisión sistemática

Palabras clave:
Biopsia repetida
Nefritis lúpica
Respuesta histopatológica
Tratamiento inmunosupresor

RESUMEN

La biopsia renal es el «estándar de oro» para el diagnóstico y la clasificación de la nefritis lúpica (NL). El papel de la biopsia renal repetida en nefritis lúpica para orientar el tratamiento o predecir el pronóstico ha sido controversial. Se llevó a cabo una revisión sistemática de la literatura basada en estudios retrospectivos y prospectivos. Los estudios se identificaron a través de bases de datos científicas electrónicas en inglés, incluyendo Medline PubMed, de publicaciones entre enero de 1990 y agosto del 2020. Los criterios de elegibilidad fueron estudios que incluyeran a pacientes adultos con NL, quienes tuvieran al menos una biopsia renal de seguimiento, con información longitudinal apropiada. Se excluyeron informes de casos, estudios con información incompleta o con pacientes duplicados. Basándose en los criterios de inclusión y exclusión, se identificaron 73 publicaciones. En la presente revisión se analizaron un total de 1.167 biopsias repetidas en pacientes con NL en 15 estudios. Las principales indicaciones para la biopsia repetida fueron: recidiva en 44-78% de los casos, y falta de respuesta en 13-51%. Adicionalmente, varias biopsias repetidas se hicieron conforme al protocolo, luego de la terapia de inducción y de mantenimiento. Con respecto a los cambios de clase histopatológica, hubo una mayor frecuencia de cambios de lesiones no proliferativas a lesiones proliferativas. Solamente dos estudios ofrecen una definición de respuesta histológica. Con frecuencia hubo cambios en el abordaje terapéutico después de realizar la biopsia repetida. Las biopsias renales repetidas son útiles en pacientes con exacerbación/recidiva y en pacientes con falta de respuesta a tratamiento. La transformación histológica fue un hallazgo frecuente; las respuestas histológicas y clínicas son discordantes. Una biopsia repetida puede ser de valor pronóstico para la toma de decisiones terapéuticas.

Introduction

Treatment response in patients with lupus nephritis (LN) is primarily assessed according to specific clinical metrics.[1] Renal biopsy is highly recommended for all subjects with suspected LN, since the biopsy allows the clinician to recognize and classify the type of renal involvement, assess its activity, and thus guide the intensity of treatment.[2,3]

Currently, the most common indication for a repeat biopsy has been to assess response one or more years after the initial diagnostic biopsy, and usually due to adverse outcomes, such as deteriorating kidney function, worsening of proteinuria, suspicion of a renal flare or suspicion of an LN class change. Some reports suggest that routinely repeating a kidney biopsy after induction therapy could be helpful to decide the next steps in LN treatment. Other authors have observed that after induction therapy, histologic and clinical responses are discordant.[1]

The usefulness of repeat kidney biopsy is still controversial; there are questions about how it impacts patient management and the risk of potential complications, mainly related to bleeding. Considering the risk-benefit ratio, some authors are reluctant to do repeat biopsies since there is no clear evidence regarding which patients undergoing a second biopsy will have clear therapeutic consequences that justify the risk.[2]

Moreover, arguments have been raised that repeat biopsies should be a standard procedure to define response after immunosuppressive treatment, thereby identifying patients who may need prolonged or intensified therapy, but also to avoid overtreatment.[4] However, the value of repeat kidney biopsy as a tool for monitoring LN is still controversial. Although renal flares and conversion from one class of LN to another are common, the need for a repeat biopsy is not yet clearly established.

The purpose of this article was to assess adult LN patients, who had at least one follow-up renal biopsy and compare it against the reference kidney biopsy, identifying the indications of repeat kidney biopsy, the histopathological transitions observed, the definition of histologic remission, and any therapeutic decisions after a repeat biopsy to establish its clinical value.

Methods

Inclusion Criteria

- Population: Patients 18 years and older with Systemic Lupus Erythematosus (SLE).
- Intervention: A reference biopsy and at least one repeat kidney biopsy. At least 2 of 4 findings: indication for repeat kidney biopsy, histopathological transition, definition of histologic remission, and therapeutic decision after repeat biopsy.
- Language: English.

- Publication dates: From January 1990 to August 2020.
- Study design: observational, descriptive and clinical trials.

Exclusion criteria

- Study design: case reports.
- Articles without access to full text.
- Duplicate patients.

Information sources and search criteria

The study was designed based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.[5] A bibliographic research was carried out from 1990 to august 2020, to find studies that met the inclusion criteria for MEDLINE PUBMED.

The Medline research was conducted via PubMed using the MeSH terms: repeat biopsy, lupus nephritis, reference biopsy, immunosuppressive treatment, histopathological response. Only articles published in English language were included.

Study selection

All studies were independently assessed by three reviewers (GAGB, SMSC and MDQ) who followed the inclusion and exclusion criteria before their consensus meeting. The information was organized using Microsoft Excel (Version 16.45).

The information collected from the selected studies included: study characteristics (authors, study design), number of patients with lupus nephritis, and renal histology categorized according to the most recent classification of the International Society of Nephrology/ Renal Pathology Society (ISN/RPS). Table 1 summarizes the variables considered in this study.

Quality and risk of bias

The QUADAS-2 tool was used to assesses the risk of bias of all the articles included. The assessment was conducted by two authors (GAGB and MDQ), who established the risk of bias by mutual agreement (Table 2).

Meta-analysis

Consideration was given to developing a meta-analysis; however, due to the homogeneity of the outcomes and the limited amount of evidence available from the studies included in this systematic review, this option was ruled out.

Results

The search identified 73 studies in MEDLINE PUBMED. 62 studies were selected after applying the filters based on the above-mentioned inclusion and exclusion criteria, and then a selection according to title and abstract led to 51 articles. Finally, 15 studies were included in the review (figure 1) and a total of 1167 repeat biopsies. Table 3 summarizes the characteristics of the studies selected from literature. This search was conducted by three authors (SMSC, MGSF and JRD).

Table 1 – Definition of Study variables.

Variable		Definition
Indication	Lack of response	Less than three months without response (no changes in proteinuria, serum creatinine and persistent active sediment) OR 6 months without partial response (improved proteinuria ≥50% and/or decreased serum creatinine ≥25%); OR one year without complete response (Proteinuria ≤0.5g/24 hrs and serum creatinine at baseline levels and non-active sediment).
	After induction	After 6 months of optimal treatment with mycophenolate or cyclophosphamide.
	After maintenance	After induction and 12-24 months of optimal treatment with azathioprine or mycophenolate mofetil.
	Relapse	Increased proteinuria (>0.5g/24hrs) OR serum creatinine (>0.2mg/dL) ± active sediment, ± hypocomplementemia ± significant increase in dsDNA titers.
	Medical criteria	Primary Rheumatologist's decision.
Histopathological transition	Proliferative to non-proliferative	Change from histological type class III, IV or mixed to class II or V.
	Non-proliferative to proliferative	Change from histological type class II or V to III, IV or mixed.
Histopathological response		Activity index (AI) in repeat biopsy of 0.
Treatment	Increase	Dose increase or switch for equivalent treatment or longer treatment time.
	Without changes	No treatment changes.
	Decrease	Dose tapering or change to maintenance treatment with a lower dose or a drug with less efficacy.
	Treatment discontinuation	Discontinue immunosuppressive treatment
Reference biopsy		Last biopsy performed against which the repeat biopsy will be compared.
Repeat biopsy		Last kidney biopsy performed for any of the aforementioned indications

Table 2 – Risk of bias based on QUADAS-2.

Study	Risk of bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference Standard
Pakozdi et al[6]	Low	Unclear	Unclear	Low	Low	Low	Low
Marinaki et al[7]	Low	Low	Low	Low	Low	Low	Low
Narvaez et al[8]	High	Low	Unclear	High	High	Low	Low
Greloni et al[9]	High	Unclear	Low	Low	Low	Low	Low
Lu et al[10]	Low	Low	Low	Low	Low	Low	Low
Pagni et al[11]	Low	Low	Low	Low	Low	Low	Low
Moroni et al[12]	Low	Low	Unclear	Low	Low	Low	Low
Daleboudt et al[13]	Low	Low	Low	Low	Low	Low	Low
Piñeiro et al[14]	High	Low	Low	High	Low	Low	Low
Tannor et al[15]	Low	Low	Unclear	Low	High	Low	Unclear
Zickert et al[16]	High	Unclear	Unclear	Low	Low	Low	Low
Parodis et al[17]	High	Low	Low	Low	Low	Low	Low
Malvar et al[18]	Low	Low	Low	Low	Low	Low	Low
Alsuwaida et al[19]	Low	Low	Low	Low	Low	Low	Low
Esdaile et al[20]	Low	Unclear	Unclear	Low	High	Low	Low

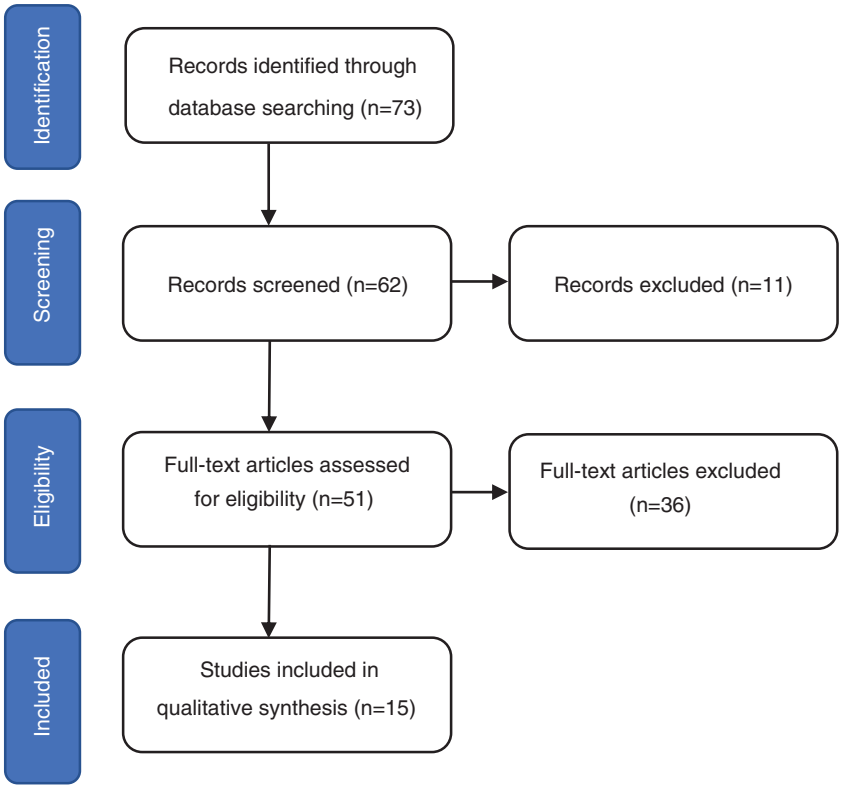

Figure 1 – Flowchart of studies selection, assessment and inclusion.

Discussion

Percutaneous kidney biopsy, introduced in the 1940s and adopted into clinical practice since the 1950s, remains the gold standard for diagnosis of LN, and is highly recommended for the identification and classification of renal involvement, to assess disease activity and thus guide intensity of treatment and also to predict prognosis.[21] Protocol repeat biopsies are sometimes controversial, but emerging data from observational cohort studies suggest that such biopsies may assist in making treatment decisions and help predict long-term renal outcomes. This systematic review discusses the indications for repeat kidney biopsy, histopathological transitions, definition of histologic remission and therapeutic decisions after repeat biopsy.

The 2019 updated European League Against Rheumatism–European Renal Association–European Dialysis and Transplant Association (EULAR/ ERA-EDTA) recommendations for the management of LN states that repeat kidney biopsy should be considered in selected cases, such as worsening of kidney variables, non-responsiveness to

Table 3 – The findings the repeat biopsy in lupus nephritis.

Author/ study design	Number of patients	Histologic class in reference biopsy n (%)	Repeat biopsy n	Indication of repeat biopsy n (%)	Histopathological transitions PL to NPL, *n* + /*n*(%) NPL to P, *n* + /*n*(%)	Histological Response	Therapeutic decisions n (%)
Pakozdi et al[6]/ retrospective cohort	238	II: 9 (12.7) III:14 (19.7) IV: 26 (36.6) III-IV + V:12 (16.9) V: 9 (12.7) No NL: 1 (1.4)	71	Relapse 50 (70.4) Lack of response 14 (19.2) NS: 7 (9.8)	4/52 (7.7) 12/19 (63.2)	No	Increase 39 (54.9) Decrease 1 (1.4) Discontinuation 2 (2.8) Without change 15 (21.1) NS: 14 (19.7)
Marinaki et al[7]/ retrospective cohort	35	II: 2 (3.4) III: 22 (37.9) IV:23 (39.7) III-IV + V:7 (12.1) V:4 (6.9%)	58	Relapse 36 (62), Lack of response 22 (38)	A. 7/52 (13.5) B. 2/6 (33.3)	No	Increase 42 (72) Decrease 3 (5) Without change 1 (2) NS 12 (21)
Narvaez et al[8]/ retrospective cohort	54	II: 9 (16.7) III:8 (14.8) IV:28 (51.9) III-IV + V:3 (5.5) V:6 (11.1)	54	NA	7/39 (18) 7/15 (46.7)	No	Increase 15 (27.7) Decrease 1 (1.9) Discontinuation 1 (1.9) Without change 37 (68.5)
Greloni et al., [9]/ retrospective cohort	45	II: 5 (11.1) III:4 (8.8) IV:22 (48.9) V: 7 (15.6) III-IV + V:1 (2.2) No NL:1 (2.2) Unknown class: 5 (11.1)	45	NS	A. 7/27 (25.9) B. 11/12 (91.6)	No	Without change 9 (20) NS 36 (80)

– Table 3 (*Continued*)

Author/ study design	Number of patients	Histologic class in reference biopsy n (%)	Repeat biopsy n	Indication of repeat biopsy n (%)	Histopathological transitions PL to NPL, *n* + /*n*(%) NPL to P, *n* + /*n*(%)	Histological Response	Therapeutic decisions n (%)
Lu et al., [10]/ retrospective cohort	156	I:1 (0.4) II:28 (11.5) III:31 (12.7) IV:88 (36.1) III-IV + V:56 (23) V:37 (15.1) VI:3 (1.2)	244	Relapse 244 (100)	61/175 (35.6) 39/66 (59.1)	No	NA
Pagni et al., [11]/ retrospective cohort	142	II: 18 (12.7) III:15 (10.6) IV: 72 (50.7) V: 24 (16.9) III-IV + V:13 (9.1)	142	Relapse 72 (50.7) Lack of response 19 (13.3) Medical criteria: 51 (36)	18/100(18) 18/42 (42.8)	No	NA
Moroni et al., [12]/ retrospective cohort	31	II:2 (5.3) III:4 (10.5) IV:23 (60.5) III-IV + V:5 (13.2) II + V:1 (2.6) V:3 (7.9)	38	Relapse 25 (65.8) Lack of response 13 (34.2)	A. 5/32(15.6) B. 5/6(83.3)	No	Increase 12 (31.6) Decrease/ Discontinuation 7 (18.4) Without change 19 (50)
Daleboudt et al., [13]/retrospective cohort	35	II:1 (2) III:6 (12.2) IV: 30 (61.3) II + V:1 (2) III-IV + V:7 (14.4) V: 3 (6.1) VI:1(2)	49	NA	A. 1/43 (2.3) B. 5/6 (83.3)	No	Increase 21 (42.9) Decrease/ Discontinuation 8 (16.3) Without change 8 (16.3) NS 12 (24.5)
Piñeiro et al., [14]/ retrospective cohort	35	III and IV:33 (94.3) IV + V: 2 (5.7)	35	Medical criteria	A. 12/35 (34.3) B. Zero	No	Increase 12 (34.3) Decrease 5 (14.3) Without change 18 (51.4)
Tannor et al., [15]/ retrospective cohort	112	II: 7 (5.5) III:23 (18.1) IV: 78 (61.4) V:19 (15)	127	Relapse 96 (75.6) After induction therapy·31 (24.4)	9/101(8.9) 9/66 (34.6)	No	Without change 57 (44.8) NS 70 (55.2)

– Table 3 (*Continued*)

Author/ study design	Number of patients	Histologic class in reference biopsy n (%)	Repeat biopsy n	Indication of repeat biopsy n (%)	Histopathological transitions PL to NPL, *n* + /*n*(%) NPL to P, *n* + /*n*(%)	Histological Response	Therapeutic decisions n (%)
Zickert et al., [16]/ prospective cohort	67	III:21 (31.3) IV:27 (40.3) III-IV + V:9 (13.4) V: 10 (15)	67	All patients after induction therapy	23/57 (40.3) zero	Yes	Increase 33 (49.2) NS 34 (50.8)
Parodis et al., [17]/ retrospective cohort	42	III-IV + V:42(100)	42	All patients after induction therapy	16/42(38.1) zero	No	Without change 33 (78.5) NS 9 (21.5)
Malvar et al., [18]/ prospective cohort	76	III: 15 (19.7) IV: 47 (61.8) III-IV + V:14 (18.5)	Bx2: 61 Bx3: 76	Bx2: after induction therapy Bx3: after maintenance therapy	NA	Yes	After of Bx3: Without change 16 (21) Increase 5 (6.6) Discontinuation 55 (72.4)
Alsuwaida et al., [19]/propective cohort	77	II:8 (10.4) III:27 (35) IV:28 (36.4) III-IV + V:6 (7.8) V: 7 (9.1) VI: 1 (1.2)	77	All patients after maintenance therapy	8//61 (13.1) 4/15 (26.7)	No	NA
Esdaile et al., [20]/ prospective cohort	87	II:2 (4.8) III:4 (9.5) IV:31 (73.8) V:5 (11.9)	42	All patients after maintenance therapy	15/35(42.8) 2/7(28.5)	No	NA
Global	1232	I: 1 (0.09) II: 91 (7.8) III: 194 (16.6) IV:523 (44.8) V: 134 (11.48) VI: 5 (0.43) II + V:2 (0.17) III + IV:33 (2.8) III-IV + V: 175 (14.9) IV + V: 2 (0.17) No NL: 2 (0.17) Unknown class: 5 (0.43)	1167	Relapse 523 (44.8) Medical criteria 86 (7.36) All patients after maintenance therapy 195 (16.7) All patients after induction therapy 140 (11.9) NS 155 (13.3) Lack of response 68 (5.8)	193/851 (22.6) 114/260 (43.8)	2/15	Increase 179 (15.3) Decrease/discontinuation 83 (7.1) Without change 213 (18.3) NS/NA:692 (59.3)

Abbreviations: Bx2: second biopsy. Bx3: third biopsy. NPL: non- proliferative lesions. PL: proliferative lesions. NA = Data not available. NL: nephritis lupus. NS = data not specified.
Narvaez et al reference biopsy was the second biopsy.
Greloni et al reference biopsy was the first biopsy and repeat biopsy were 71.
Piñeiro et al, Malvar et al and Parodis et al only include proliferative class or mixed.
Zickert et al didn't include class II.
Parodis et al included 8 from Euro-Lupus and 25 from MAINTAIN.

immunosuppressive or biologic treatment or relapse, to demonstrate possible histologic class transition or changes in chronicity and activity indices; to provide prognostic information; and detect other pathologies.[22]

The primary indications for repeat biopsy were identified as relapse (44-78%) and lack of response (13-51%). Pagni et al [11]also mentioned as an indication of repeat biopsy the potential reduction of immunosuppressive therapy. In some studies, repeat biopsy was performed per protocol after induction and maintenance therapy.[15–20] Protocol biopsies have taught us some important lessons. Although very few studies have been conducted with repeat biopsy immediately after induction treatment, findings from such biopsies suggest that repeat biopsies are more predictive of long-term kidney and patient outcomes than reference biopsies. Furthermore, such biopsies showed that aggressive immunosuppression and rapid control of clinical disease activity did not necessarily prevent chronic damage in LN. Thus, the clinical findings after induction therapy may not reflect what is happening in the kidney regarding inflammation and chronic damage.

One study of patients with proliferative LN, where renal biopsies after induction treatment were done per protocol, showed that one-third of patients with complete clinical response still had high histologic activity on the second biopsy, and that 62% of patients with complete histologic remission on re-biopsy still showed persistent clinical activity. The results show that after induction therapy, histologic and clinical responses are discordant.[23]

Repeat biopsy after maintenance treatment has also shown continuing histologic activity in a significant number of patients. The discontinuation of maintenance immunosuppression in such patients may put them at risk of renal flare. In a study, 44% of the patients were found to have persistent histologic activity.[24] These data demonstrate that despite extensive and long-term immunosuppression, patients with LN who go into complete clinical renal remission still have a high relapse rate following withdrawal of maintenance immunosuppression. Relapse-prone patients cannot be identified a priori by clinical or demographic variables. However, examination of kidney histology during treatment and after clinical remission provides useful information to predict who is likely to relapse and who is likely to remain in remission after discontinuation of immunosuppression[24,25].

It is well known that LN class may change to a different grade during flares. Nevertheless, a repeat biopsy during LN flare remains controversial as some research has shown that proliferative LN on the first/reference biopsy does not commonly change to non-proliferative LN during flare. Therefore, treatment adjustments may initially be made based on clinical and laboratory signs. It has been shown that clinically relevant class switches are more frequently observed in patients with nonproliferative lesions, ranging from 26 to 91%; however, as expected, patients who initially had proliferative lesions rarely switched to nonproliferative nephritis, ranging from 3 to 40%. Based on these data, a repeat biopsy would allow for the identification of patients with proliferative changes who transitioned to a non-proliferative class or vice versa. A second biopsy showing chronicity or inactive disease may also help in guiding immunosuppressive reduction.

Very few studies [16,18]provide a definition of histological response; these studies have shown discordance between clinical and histologic findings in patients with LN who have undergone protocol kidney biopsies during induction or maintenance therapy. Most studies show the mean AI both in reference biopsies and in repeat biopsies; however, they fail to specify how many still have AI > 0.

The therapeutic decision after repeat biopsy shows that in many studies treatment changes are introduced. However, as mentioned above, patients with complete histological recovery may have persistently abnormal clinical findings, suggesting that repeat biopsies may be a valuable tool to guide the decision to withdraw immunosuppressive therapy. Furthermore, discontinuing immunosuppression in patients with ongoing marked renal inflammation may put them at risk of renal relapse, while continuing treatment in patients with signs of clinical activity (proteinuria) but with no histological activity, may expose patients to increased morbidity from unnecessary immunosuppression.[26]

There are some limitations to this systematic review including the retrospective nature of the studies which focused on indications of repeat kidney biopsy, histopathological transitions, the definition of histologic remission, and the therapeutic decision after repeat biopsy. Morevoer, the study fails to assess the association among the clinical, laboratory and histopathological characteristics; few studies show the relationship between clinical and histopathological response, and long-term outcomes. Furthermore, most studies fail to provide treatment details before repeat kidney biopsy.

Conclusions

The current data suggest that a repeat biopsy should be considered in patients with LN flare/relapse, especially when the reference biopsy was ISN/RPS class I/II or V, as histology changes are likely to impact treatment options. A repeat biopsy should also be considered in patients with poor treatment response as a tool to guide treatment choices and eventually discontinuing or tapering immunosuppression. Histological transformations are common. Treatment changes are introduced following a repeat biopsy. The repeat biopsy could have prognostic value for therapeutic decision-making.

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Conflict of interest

The authors have no conflict of interest to disclose.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2021.02.003.

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