



Review Article

Rituximab in Lupus Nephritis: A Non-systematic Review[☆]

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ARTICLE INFO

Article history:

Received 14 July 2015

Accepted 15 January 2016

Available online 21 June 2016

Keywords:

Rituximab

Nephritis

Lupus

Palabras clave:

Rituximab

Nefritis

Lupus

ABSTRACT

Lupus nephritis (LN) is a common and severe complication in patients with lupus. Current therapy is based on immunosuppressive drugs and glucocorticoids. Recently, rituximab has been proposed as an alternative treatment for LN. Rituximab is a monoclonal antibody directed against the CD20 antigen receptor on B cells. The aim of this review is to summarize all the available information about rituximab in LN. Eleven studies were found; three of them were observational studies (2 prospective and 1 retrospective) and eight were clinical trials (7 open-label studies and only 1 randomized controlled trial [RCT]). The evidence is insufficient to establish the role of rituximab in the treatment of LN. Results from the only RCT, which were negative, suggest a clinical benefit in black people. Further studies must confirm this hypothesis. Controlled clinical trials involving adaptive randomization are required to establish the real benefit of rituximab in LN.

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Rituximab en nefritis lúpica: una revisión no sistemática

RESUMEN

La nefritis lúpica (NL) es una complicación común y grave del lupus. En la actualidad, la terapia está basada en inmunosupresores y glucocorticoides. Recientemente se ha planteado como posible tratamiento al rituximab, un anticuerpo monoclonal dirigido contra el antígeno CD20 de los linfocitos B. El objetivo de la presente revisión es recopilar la información disponible hasta el momento acerca del uso de rituximab en NL. Se encontraron 11 estudios, 3 observacionales (2 prospectivos y uno retrospectivo) y 8 ensayos clínicos (7 abiertos y solo uno aleatorizado controlado). La evidencia es insuficiente para establecer el papel del rituximab en la terapia de la NL. Resultados del único ensayo clínico aleatorizado y controlado, el cual falló en demostrar una mejoría clínica significativa, indican un posible beneficio en pacientes de raza negra. Futuros estudios deben confirmar dicha hipótesis. Se proponen ensayos clínicos controlados, con aleatorización adaptativa, para establecer el verdadero beneficio con rituximab en NL.

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Introduction

Lupus nephritis (LN) is a common but serious complication of systemic lupus erythematosus (SLE). The prevalence of SLE ranges between 1.4% and 21.9% and the incidence between 7.4 and

159.4 cases per 100 000 population.¹ It is known that 60% of the SLE patients will develop LN² and more than 25% of these patients will develop end-stage renal disease 10 years after the onset of renal symptoms.¹

The main clinical features are proteinuria and microscopic hematuria. Less common findings are macroscopic hematuria and hypertension.² Certain histopathological changes can result in different clinical presentations. Thus, although in LN, the histopathological findings obtained from renal biopsy are not necessary for the diagnosis, they are of the utmost importance for the classification of the disease.

[☆] Please cite this article as: Zurita Gavilanes L, Costa Valarezo A. Rituximab en nefritis lúpica: una revisión no sistemática. Reumatol Clin. 2016;12:210–215.

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Different pathophysiological mechanisms have been involved in the development of LN in SLE patients. A combination of genetic, environmental and immunological factors mediate the processes that result in the renal damage.^{1–4} Of special importance for the present review is the role of the B cells, which are hyperactive in SLE. The B cells mediate and regulate antibody production, interact with memory T cells and stimulate proinflammatory cytokine production, all of which makes them essential components of the pathophysiology of LN.¹ It is for these reasons that the use of rituximab is proposed. Rituximab is a chimeric monoclonal antibody (murine/human) approved by the United States Food and Drug Administration in 1997.⁵ This monoclonal antibody is directed against CD20, an antigen expressed on the surface of mature and immature B cells. CD20 regulates the initiation of the cell cycle. The binding of the antibody to Fc receptor induces apoptosis and cytotoxicity, mediated by both complement and antibodies.

Treatment of LN was based for some years on glucocorticoids. This therapy had the disadvantage of the high morbidity and mortality rates resulting from the high doses administered, as well as its inability to arrest the progression of the renal disease.⁶ One proposal for solving this problem was the use of immunosuppressive agents, which were evaluated in a landmark clinical trial performed to determine the long-term survival of 107 LN patients. This trial revealed a difference in terms of renal function preservation, but said difference was statistically significant only for the combination of intravenous (IV) cyclophosphamide and low-dose, rather than high-dose, prednisone. No differences in the mortality rate were observed.⁷

At the present time, therapy for LN consists of an induction phase followed by a maintenance phase. The majority of the patients with active proliferative LN are initially treated with pulsed methylprednisolone for 3 days, followed by a period of oral prednisone at an initial dose that is tapered until it reaches the minimum effective dose. The guidelines for the management of LN of the American College of Rheumatology recommend oral mycophenolate mofetil (2–3 g/day) or intravenous cyclophosphamide, together with glucocorticoid therapy as induction therapy for classes III and IV LN (level A evidence).⁸ In general, high doses of intravenous cyclophosphamide (500–1000 mg/m² each month for 6 months), although the results observed with lower doses of intravenous cyclophosphamide (500 mg/m² every 2 weeks for 6 months) were similar to those of the high-dose regimen.⁹ The recommendation for maintenance therapy is the use of mycophenolate mofetil or azathioprine. The choice of one or the other should be made on an individual basis.

Resistance to standard induction therapy and recurrences during treatment have led to the consideration of new therapeutic strategies that include the use of rituximab as a third line of treatment, especially in focal or diffuse proliferative LN, the clinical courses of which are more aggressive than those of other classes of LN. It is difficult to determine the incidence of resistance to the initial treatment in LN patients simply because it is difficult to determine remission in these individuals, as this concept varies depending on the criteria applied. In general, remission has been confirmed by the presence of inactive urinary sediment, reduced proteinuria and normalization of the serum creatinine level. On the other hand, treatment resistance is defined as the failure to respond after 6 months of glucocorticoid and immunosuppressive therapy.⁸ The first step in patients who fail to respond to the initial treatment will depend on the immunosuppressive agent being used and will consist in switching to another immunosuppressive medication. Thus, if cyclophosphamide was being administered, it should be replaced by mycophenolate mofetil and vice versa. If this strategy were to fail to achieve remission, the use of rituximab is proposed (level C evidence).⁸

The LUNAR study (A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis)¹⁰ is the first randomized, parallel-group, placebo-controlled clinical trial to incorporate rituximab into therapy for LN, in combination with glucocorticoids and mycophenolate mofetil. Its publication in 2012 raised great expectation, as its results would confirm those observed in previous studies.

The purpose of the present literature review is to retrieve the most recent publications on the advances and data concerning the use of rituximab in LN, to provide the available information and perform a critical analysis of the limited evidence supporting this information.

Methodology

We conducted a literature search in the MEDLINE and Cochrane databases using the MeSH terms “lupus nephritis/drug therapy” and “rituximab”. We each performed a separate search, using filters so that only those studies defined as “clinical trial”, “multicenter”, “randomized controlled” or “comparative” were retrieved. We also selected observational studies, meta-analyses and/or systematic reviews using search filters. The search in the MEDLINE database yielded 11 studies^{10–20} involving humans published between 1 January 2000 and 30 May 2015. Of the 11, 3 were observational (2 prospective^{11,12} and 1 retrospective¹³). The remaining 8 were clinical trials (7 were open-label^{14–20} and only 1, the LUNAR study,¹⁰ was randomized, parallel-group and placebo-controlled). We included those observational or experimental studies that involved LN patients—and those involving SLE patients in which a subgroup of LN patients was analyzed—and were designed to evaluate partial and complete remissions in response to treatment with rituximab. One of the open-label clinical trials was excluded because it included only 1 patient.¹⁵ We obtained a Cochrane database review.²¹ The bibliography of each of the selected studies was reviewed in search of other relevant articles; moreover, additional information was sought in the UpToDate™ database using the terms “nephritis lúpica” and “rituximab”. This additional search in the UpToDate™ database yielded no more studies of interest and the information was used as a reference resource for other sections of this review. The exclusion of the article by Fra et al.¹⁵ left a total of 10 studies.

Rituximab in Observational Studies

The characteristics of the observational studies retrieved are summarized in [Table 1](#).

In their retrospective study, Melander et al. included 20 patients who received rituximab as induction therapy for class IV and class V LN, with a follow-up of less than 12 months.¹³ Remission was finally achieved in 12 patients (60%): 7 complete and 5 partial. Rituximab was administered as first-line treatment in only 2 patients. In this study, the normalization of the glomerular filtration rate was used as a criterion for complete remission (≥ 60 mL/min/1.73 m²).

In 2010, Terrier et al.¹² published a prospective study in France, in which they analyzed the data of the French Autoimmunity and Rituximab Registry. This registry invites the hospitals of France to participate in order to analyze those patients with autoimmune diseases refractory to treatment who are receiving rituximab. In 42 patients with LN (class IV in the great majority), renal response was achieved in 23 of 31 patients with available data for this category. Of these 23 patients, 14 (45%) experienced a complete remission and 9 (29%), partial remission. Proteinuria was markedly reduced, although the serum creatinine level remained stable. However, as the registry is for SLE in general, it does not provide specific data

Table 1
Characteristics of the Observational Studies With Rituximab.

Author/year	Population	No. of patients (mean age [years])	Treatment-naïve patients (%)	Protocol of RTX administration	Mean follow-up period	Main outcomes (P value)
Melander et al. ¹³ 2009 ^{a,b}	III-V LN according to biopsy	20; 95% W (25.6)	10	375 mg/m ² × 4 in 90% of patients	22 months	CR: 35%; PR: 25%
Terrier et al. ¹² 2010 ^c	SLE, 31% con LN; 19% class III and 52.4% class IV (95% biopsy)	42	24	Dose in LN patients of the registry not reported	16.6 months	CR: 45% (.0001); PR: 29% (.004)
Condon et al. ¹¹ 2013 ^d	III-V LN according to biopsy	50; 78% W (45)	58	1 g × 2 (with 0.5 g MPS)	40.75 months	CR: 72%; PR: 18%

CR, complete remission; GFR, glomerular filtration rate; LN, lupus nephritis; MPS, methylprednisolone; PR, partial remission; RTX, rituximab; SLE, systemic lupus erythematosus; UPC, urinary protein to creatine; W, women.

^a Retrospective observational study.

^b PR, 24-h proteinuria >50% and stabilization of the GFR; CR, proteinuria <0.5 g/day, absence of hematuria and GFR ≥ 60 mL/min/1.73 m² or improvement of 50% over the basal GFR value.

^c PR, improvement by 50% in all the renal parameters (serum creatinine and proteinuria); CR, decrease in proteinuria to 0.5 g/day, disappearance of hematuria and normalization of GFR.

^d CR, combination of a UPC ratio less than 50 mg/mmol and serum creatinine no greater than 15% of baseline level; PC, UPC ratio <300 mg/mmol with a reduction >50% with respect to the baseline level and an increase in serum creatine no greater than 15% over the baseline level.

on LN patients (for example, neither the dose nor the protocol for rituximab administration is reported).

An observational cohort study in which the purpose was to exclude glucocorticoids from the treatment in patients with LN showed that the combination of rituximab and low-dose intravenous methylprednisolone for induction and mycophenolate mofetil for maintenance, without oral glucocorticoids, is also an effective treatment, as remission was achieved in 60% of the patients.¹¹ For the first time in 60 years, a study showed that oral glucocorticoids can be avoided without compromising treatment efficacy in LN. The randomized controlled clinical trial RITUXILUP (NCT01773616), which is in the recruitment phase, was designed to evaluate the efficacy of this protocol.

Open-label Clinical Trials With Rituximab

In 2006, Vigna-Perez et al.¹⁶ treated 22 patients with LN with 0.5–1 g of rituximab on days 1 and 15 of induction therapy, together with immunosuppressive agents. Most of the patients had disease that was refractory to the previous treatment. Seven patients (31.8%) had a partial remission and 5 (22.7%), complete remission. Moreover, the authors reported improvement in the disease activity index in 90% of the patients, reduced proteinuria as early as day 15 in some, B-cell depletion, and stimulation of the regulatory function of the regulatory T cells (Treg), with no significant adverse effects. Gunnarsson et al.¹⁷ reported a change in the histopathological findings in 7 patients with LN in whom biopsies were performed at the start of the study and 6 months later. A change in the histological classification was observed in all the patients. The disease activity index decreased dramatically after 6 months of treatment with rituximab. Complete and partial remissions were achieved in 2 patients and in 1 patient, respectively.

In a parallel-group clinical trial,¹⁸ treatment with rituximab alone was compared with the combination of rituximab and cyclophosphamide in 19 patients. No significant difference in clinical efficacy was observed between the 2 groups in terms of the rate of remission. Partial and complete remission was achieved in 11 and 4 patients, respectively. On the other hand, in another study,¹⁹ with a much longer follow-up period and a larger number of patients, the response to rituximab in combination with cyclophosphamide was evaluated in patients with disease refractory to standard therapy for a mean period of 36 months. Renal and histopathological responses were achieved within the first year, although, in many of the patients, these responses occurred at year 2. Low CD19+ B cell counts and IgM levels were correlated with a shorter time

to response, and the duration of B-cell depletion was positively associated with time to response.

Davies et al.¹⁴ report the rates of remission in 18 patients with disease refractory to standard therapy after 6 months of treatment with rituximab in combination with cyclophosphamide. Eleven patients achieved complete remission and 2, partial remission. We should point out that this study provides information on the patients who showed absolutely no response. The nonresponders experienced considerable renal deterioration, as shown by the histological grade. Class IV–G LN may be particularly associated with a poor response to therapy.

The most recent study of Moroni et al.,²⁰ published in 2014, which compared 3 treatments groups, 1 with rituximab, another with cyclophosphamide and a third with mycophenolate mofetil, showed rituximab to be at least as effective as the immunosuppressive agents for induction therapy. As the editorial referring to the aforementioned article indicates, although this study gives us an idea of the role of rituximab in LN, randomized trials with high-level evidence are necessary in order to corroborate these findings.²² The main characteristics of the open-label clinical trials are shown in Table 2.

A recent systematic review and meta-analysis,²³ which included 30 open-label studies—involving a total of 1242 patients diagnosed with SLE—only 11 of which (201 patients) dealt specifically with LN and rituximab, found an overall rate of renal remission of 72.1% (95% confidence interval [CI], 64.3%–78.8%). The analysis of 10 studies that reported complete and partial remissions demonstrated complete remission in 36.1% (95% CI, 25.2%–48.6%) and partial remission in 37.4% (95% CI, 28.5%–47.3%) of the patients studied. A noteworthy aspect of this review with meta-analysis is the lack of consensus in the evaluation of SLE, as well as the discrepancy between observational studies and clinical trials with respect to the efficacy of rituximab, which we also observed in the present review.

Rituximab in a Randomized Placebo-controlled Clinical Trial: the LUNAR Study

The evidence available up to 2012 supports the use of rituximab as “rescue” therapy rather than initial therapy.²⁴ The LUNAR study is the only parallel-group, placebo-controlled clinical trial that randomized 144 patients with class III or IV LN to receive mycophenolate mofetil, glucocorticoids and rituximab or to receive mycophenolate mofetil, glucocorticoids and placebo. This study included patients from the United States (74%) and from Latin America (26%), and the primary end point was the renal response

Table 2
Characteristics of the Clinical Trials With Rituximab.

Author/year	LN classification (%)	Response to treatment at the time of RTX therapy	No. of patients (mean age in years)	Comparator	Treatment	RTX administration protocol	Evaluation time points	Results
Vigna-Perez et al. ¹⁶ 2006 ^a	III (9.1); IV (81.8); V (9.1)	Disease refractory to treatment Recurrence (9.1%)	22; W 86.4% (29)	No	RTX+IST	0.5–1 g day × 2	Days 30, 60 and 90	CR: 31.8%; PR: 22.7%
Gunnarsson et al. ¹⁷ 2007 ^b	III (14.3); IV (85.7)	Disease refractory to treatment	7; W 100% (30)	No	RTX+IST	375 mg/m ² × 4	6 months	CR: 42.9%; PR: 14.3%
Li et al. ¹⁸ 2009 ^c	III (10.5); IV (15.8); III+IV (5.3); III+V (63.2); IV+V (5.3)	Not reported	RTX: 9 (40.3); RTX+CYC: 10 (39.6)	Yes	RTX vs RTX+CYC	1 g × 2	Every month for 6 months, every 2 months thereafter for 48 weeks	CR: 21%; PR: 58%
Davies et al. ¹⁴ 2013 ^b	III (27.8); IV (27.8); V (11.1); IV+V (22.2); III+V (11.1)	Disease refractory to treatment	18; W (–)	No	RTX+CYC	1 g × 2	6 months	CR: 61.1%; PR: 11.1%
Jónsdóttir et al. ¹⁹ 2013 ^d	III or IV (60); V (36)	Most patients with disease refractory to treatment	25; W 92% (34.5)	No	RTX+CYC	375 mg/m ² × 4	Every 2–3 months the first year, every 6 months thereafter. Mean follow-up 36 months	CR: 64%; PR: 24%
Moroni et al. ²⁰ 2014 ^e	III (16.6); IV (48.1); V (3.7); III+V (9.3); IV+V (18.5)	50% no treatment, 40.7% recurrence and 9.3% disease refractory to treatment	MMF: 17 (32.4); RTX: 17 (31.1); CYC: 20 (31)	Yes	RTX vs CYC vs MMF	1 g × 2	12 months	CR: 70.6%; PR: 29.4%
Rovin et al. ¹⁰ 2012 LUNAR ^f	RTX: III (34.7); IV (65.3); V alone or in combination (36.1). PCB: III (33.3); IV (66.7); V alone or in combination (31.9)	No treatment for LN	RTX: 72; W 87.5% (31.8). PCB: 72; W 93.1% (29.4)	Yes (PCB)	MMF+PCB vs MMF+RTX	1 g × 4	Response at 52 weeks	CR: 26.4%; PR: 30.6%. P = .55

Cr, serum creatinine; CR, complete remission; CYC, cyclophosphamide; IST, immunosuppressive therapy; LN, lupus nephritis; MMF, mycophenolate mofetil; PC, partial remission; PCB, placebo; RTX, rituximab; SLICC, Systemic Lupus International Collaborating Clinics; UPC, urinary protein to creatinine; W, women.

^a CR, normal Cr, inactive urinary sediment, proteinuria <0.5 g/day; PR, improvement >40% in renal parameters compared to the beginning of the study.

^b CR, normal Cr, normal serum albumin, inactive urinary sediment, albuminuria <0.5 g/day; PR, improvement ≥50% in renal parameters compared to the beginning of the study.

^c CR, if the baseline SLICC disease activity index was >0 and was reduced to 0 after follow-up; PR, if the baseline SLICC disease activity index was higher than the index after follow-up, but the latter was not equal to 0.

^d Response to treatment (CR and PR), defined in accordance with the 2009 European Consensus Statement on LN.

^e CR, Cr <1.2 mg/dL (or return to the baseline value in patients with chronic kidney disease) and proteinuria <0.5 g/day and <5 urinary red blood cells/high power field; PR, Cr <1.2 mg/dL (or return to the baseline value in patients with chronic kidney disease) and proteinuria of 0.5–2 g/day.

^f CR, normal Cr if it was abnormal at the beginning of the study, or a Cr level ≤115% of baseline if it was normal at the beginning of the study; inactive urinary sediment (<5 red blood cells/high power field and absence of red blood cell casts), and UPC ratio <0.5; PR, Cr ≤ 115% of baseline, urinary red blood cells/high power field ≤50% above baseline and no red blood cell casts, and a decrease of at least 50% in the UPC ratio to <1.0 (if the baseline UPC ratio was ≤3.0) or to ≤3.0 (if the baseline UPC ratio was >3.0).

in terms of complete or partial remission 52 weeks after adding rituximab to the treatment. Despite the fact that the results with rituximab were favorable, they were not statistically significant. In all, 45.8% of the patients in the placebo group achieved remission (either partial or complete). The rate of remission in the rituximab was 56.4%, but the difference was not statistically significant ($P = .18$). Although no difference could be demonstrated, the authors found that, among black patients, the rate of remission with rituximab was 70% vs 45% in the placebo group. This difference, while not significant ($P = .20$), indicates both the possible efficacy in this subgroup of patients and the need to undertake a randomized, controlled trial involving only black patients, whose prognosis is poorer than that of other subpopulations.

We could attribute this failure, in terms of the statistical difference in the results, to the short follow-up, or even to the small sample size; however, it may be that the response is much more practical and that the addition of rituximab simply is not effective in a therapy that, in itself, is highly effective.

There is an interesting difference between the study conducted by Terrier et al. based on the French Autoimmunity and Rituximab Registry and the LUNAR study. The difference in the proportion of patients who were resistant to mycophenolate mofetil and/or cyclophosphamide in the 2 studies is enormous (76% vs 0%). Perhaps this indicates that rituximab is effective when administered to patients who do not respond to standard therapy. A controlled study of patients with LN that is refractory to standard treatment would be highly interesting.

A review published by Blüml et al.,²⁵ which details the clinical use of B-cell-targeted therapies, establishes an important principle with the premise that the use of an agent, like mycophenolate mofetil, that interferes with B-cell differentiation can, in a way, mask the effect of rituximab. Mycophenolate mofetil was used in the LUNAR study, a fact that may, in part, explain the results. Another possible hypothesis concerns the mechanism of action of rituximab, as this agent is effective in producing a depletion of circulating B cells without affecting those of the mantle or the marginal zone and, it is thought, that the latter two could continue to mediate inflammation.²⁶ The more we know about the molecular mechanisms of the diseases, the closer we get to knowing the therapeutic objectives. Apparently, the treatment of LN requires a complete understanding of the molecular interactions that mediate its pathogenesis. It is known that B-cell depletion promotes the production of B-cell activating factor; this factor generates new autoreactive B cells. This mechanism could in some way explain the failure of rituximab therapy. The B regulatory cells (Breg) modulate the inflammatory response mediated by the B cells. Studies in mice have shown that rituximab results in the depletion of this B-cell line.²⁷

In a systematic review more recent than the LUNAR study, the clinical efficacy of rituximab is analyzed in 26 reports, including prospective and retrospective studies, case series and case reports.²⁸ The authors found that, of the patients being treated with rituximab, 40% achieved complete remission after 60 weeks and 34% achieved partial remission during the follow-up period. Once again, we observe that rituximab is effective when it is administered after standard therapy has failed and when there is resistance to other drugs. The review details the percentage of patients who respond with rituximab in each LN class. Rituximab is found to be more effective in class III LN (60%). The efficacy of rituximab in refractory LN is being evaluated in the RING study (Rituximab for Lupus Nephritis with Remission as a Goal, NCT01673295), which includes patients who have no response to standard treatment after 6 months.

Despite the lack of conclusive evidence, physicians utilize rituximab in routine clinical practice on the basis of their personal experience and the open-label studies that demonstrate the

efficacy of this agent.²⁹ Future studies will probably be able to provide quality evidence that will have an impact on clinical practice, and lead to the reconsideration of the management guidelines concerning the use of rituximab in LN.

Conclusion

Observational and open-label studies have reported that the monoclonal antibody rituximab has high clinical efficacy in the treatment of LN, which is a serious complication and an indicator of poor prognosis in patients with SLE.

A controlled study conducted to confirm its efficacy failed to demonstrate a statistically significant difference attributable to the addition of rituximab to standard therapy in terms of an improvement in the rate of remission in LN patients. These results are discouraging as this nephropathy continues to be associated with high rates of mortality and morbidity due to end-stage renal failure and the severe toxicity and the adverse effects of the drugs that, to date, are being administered for the current treatment of LN. The lack of response observed in controlled studies may be due to the variability of the clinical signs of SLE, as well as to the efficacy of the medications permitted in the study, which could have masked the results.

Patients who show resistance to the standard initial treatment usually experience a better response when rituximab is added. This monoclonal antibody may prove to be highly beneficial in those patients, especially in blacks. A randomized, double-blind, controlled study is necessary to confirm its clinical efficacy.

At this point, rituximab should not yet be excluded from the group of agents that are to be tested for their potential contribution to the medical management of LN. The target is to be able to discard the glucocorticoids and achieve greater efficacy in terms of the rate of complete remissions. Therapy targeting B-cell depletion will probably consist in much more than the administration of a single drug; in view of the immune mechanisms that play a role in the pathogenesis of LN, it would be necessary to establish a strategy to block the compensatory mechanisms and inhibit the unwanted effects of rituximab, in order to optimize therapy involving this drug. At this time, there is no conclusive evidence (systematic reviews with or without meta-analyses^{21,23,28}) that supports the use of rituximab as part of the first-line therapy in LN, and the recommendation for the use of this agent as third-line therapy comes from open-label studies with low statistical power, as has been detailed in this review. It will be necessary to perform randomized, double-blind, placebo-controlled clinical trials that preferentially utilize the so-called adaptive randomization, in which patient allocation varies in favor of the group showing the best outcome over the course of data collection. Likewise, the subgroup of black patients is of special interest as this subpopulation showed a difference, although not statistically significant, indicating the potential benefit of a clinical trial designed to confirm the benefit of rituximab particularly in this group.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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