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The clinical efficacy of Rituximab in patients with lupus nephritis. A single-center observational study

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Abstract

Introduction: Lupus Nephritis is a common and severe complication of systemic lupus erythematosus. Therapy based on immunosuppressants and glucocorticoids has recently been proposed as a possible treatment for Rituximab, but the evidence on its efficacy is limited.

Methods: The present observational study was carried out at the José Carrasco Arteaga Hospital (Cuenca-Ecuador) in patients with lupus nephropathy treated with Rituximab in 2018. Efficacy was evaluated with creatinine clearance and proteinuria measurement. Demographic characteristics are described, and the Wilcoxon test was used for comparisons.

Results: 28 cases were analyzed; 78.6% were women, 38.3 years old, and 35.7% had membranous lupus nephritis (class V). The creatinine and creatinine clearance values did not present significant variations at three, six, nine, and twelve months. The 24-hour proteinuria values were significantly lower after the administration of Rituximab; from the third month, significant changes are observed that are maintained at six, nine, and 12 months.

Conclusion: Rituximab, as part of the treatment of Lupus Nephritis, has a stabilizing effect on creatinine and creatinine clearance values, that is, without disease progression, with a significant decrease in proteinuria.

Keywords:

MESH: Lupus Nephritis; Rituximab; Proteinuria; Renal Insufficiency, Chronic; Glomerular Filtration Rate; Disease Progression.

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Email: Miriam Gabriela Méndez Quizhpi <gabymendez1894@gmail.com>/Address: Av. Paraíso Y Che Guevara, Campus Paraíso, School of Medicine, University of Cuenca. Ecuador basin. Telephone: (593) 07 405-1000 REV SEN. 2022 ;10 (2):130-136 |

Systemic lupus erythematosus (SLE) is an autoimmune, chronic disease that affects different organs, among them, and the most affected is the renal system, becoming a serious complication called lupus nephritis (LN), with a prevalence in more than 30% of patients with SLE. The cause is unknown, and it preferentially affects women of childbearing age. However, it can appear at any age, regardless of race. Its presence increases mortality and morbidity in patients with SLE, mainly due to the risk of transcending to chronic kidney disease, requiring renal replacement treatment in approximately 25% of patients [1].

In the United States, 30% of patients with SLE evolve to clinical manifestations of nephritis at the time of diagnosis, and of these, between 50% and 60% develop it during the first ten years of the disease; there is a prevalence between 5 and 10% more significant in African Americans and Hispanics compared to Caucasians, with male sex being a higher risk factor for developing lupus nephritis (M/F: 47.85/30.91%, P <0.001) in addition to young adults (P <0.001)[2, 3].

Currently, the pharmacological treatment of lupus nephritis is divided into two phases, one for induction and the other for maintenance. The American College of Rheumatology recommends using intravenous mycophenolate mofetil or cyclophosphamide and glucocorticoid therapy as induction therapy. For the maintenance phase, mycophenolate mofetil or azathioprine is used, considering that the choice of medication must be individualized for each patient [3].

Due to resistance to induction treatment and recurrence, new therapeutic strategies have been considered, such as rituximab (evidence level C), a third-line treatment especially indicated in the presence of focal or diffuse proliferative LN since its clinical presentations are aggressive [3].

Rituximab is a chimeric monoclonal antibody; it represents the third-line treatment in the disease. It is mainly used during the induction phase in patients with class IV and class V LN or patients refractory to treatment, which is why it has been used in recent years. However, in the Ecuadorian context, there are few studies on the efficacy of rituximab, and it is unknown if this therapy is effective in patients with LN, for which the following question has been raised: What is the efficacy of rituximab based on the values of proteinuria and creatinine clearance in patients with lupus nephritis at José Carrasco Hospital? Arteaga, during 2018?, We proposed an observational study to resolve this question to describe rituximab's efficacy in treating LN.

Materials and methods

Study design

The present study is observational, descriptive, and longitudinal. The source is retrospective.

Scenery

The study was carried out in the nephrology department and the biological administration area of the José Carrasco Arteaga Specialty Hospital of the Ecuadorian Institute of Social Security in Cuenca-Ecuador from January 1, 2018, to January 30, 2018. December 2018.

Participants

Patients with a histological diagnosis of lupus nephropathy evaluated in the outpatient clinic of the institution who were admitted for immunosuppressive treatment were included. Minor patients were excluded. Cases with incomplete data for analysis, incomplete medical records, or without follow-up after admission were eliminated.

Variables

The variables were sex, age, weight, class of lupus nephritis, plasma creatinine, creatinine clearance, and proteinuria.

Data sources/measurements

The source was indirect; the institutional electronic file, the registry of statistical services, nephrology, outpatient consultation, and biological administration area were reviewed. The glomerular filtration rate (GFR) in this study was estimated by calculating creatinine clearance with the CKDPI formula.

Biases

To avoid possible interviewer, information, and memory biases, the principal investigator kept the data at all times with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

Study size

The sample was nonprobabilistic, census type, where all possible cases from the study period were included since there is a low prevalence of LN in immunological treatment.

Quantitative variables

Descriptive and inferential statistics were used. The results were expressed on a scale of means and standard deviation. Categorical data such as sex are presented as proportions.

Statistical analysis

Noninferential and inferential statistics are used. For the descriptive analysis, measures of central tendency and dispersion were calculated according to the measurement scale of each of the variables. Qualitative variables will be presented with absolute

numbers and percentages; for the quantitative variables, the median is a measure of central tendency, and the minimum and maximum values are measures of dispersion.
Inferential analysis: The comparison between the two groups was made with the Wilcoxon rank test. The statistical significance level was $P < 0.05$. The statistical package used was SPSS 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Participants

Twenty-eight patients were studied.

Baseline characteristics of the study population

There were six men (21.4%) and 22 women (78.6%), with an age of 38.36 ± 11.6 years and a weight of 63.3 ± 14.8 kilograms. The distribution by age and weight in categorical distribution is presented in Table 1. The prevalence of membranous LN was higher; however, the proliferative states from grade I to IV corresponded to 17 cases. Only 1 case consisted of sclerosing nephritis (Table 1).

Table 1. Description of the population according to age, weight, and NL class.

	n=28	%
Age		
20-29 years	9	32.1%)
30-39 years	4	14.28%
40-49 years	12	42.85%
50-59 years	1	3.57%
>60 years	2	7.14%
Weight		
40-59 kg	13	46.4%
60-79 kg	11	39.3%
80-99 kg	3	10.7%
>100 kg	1	3.6%
NL class		
I: Minimal Mesangial Nephritis	1	3.6%
II: Proliferative Mesangial Nephritis	4	14.3%
III: Focal Proliferative Nephritis	8	28.6%
IV: Diffuse Proliferative Nephritis	4	14.3%
V: Membranous Nephritis	10	35.7%
VI: Sclerosing Nephritis	1	3.6%

*LN: lupus nephropathy

Serum creatinine and glomerular filtration rate

The 12-month averages of creatinine values remain the same without reporting a significant variation; likewise, creatinine clearance values remain within similar ranges. A comparison was made between the pre- and postsituation creatinine levels using the nonparametric Wilcoxon signed-rank test. No significant changes are observed in the values; however, as time passes, nonsignificant variations are observed. When making cuts in the values considered normal for creatinine, it was noted that in 6 patients who presented values outside the standard ranges prior to the administration of rituximab, no significant changes were observed three, six, nine, and twelve months later. (Figures 1 and 2)

Figure 2 shows the glomerular filtration rate. Compared with the Wilcoxon signed rank test regarding the Clearance values, nonsignificant variations are observed at three, six, nine, and twelve months. Therefore, the values are similar in the previous situation as in the months after the start of treatment with rituximab. The clearance level decreased in 11 patients and did not present significant changes with the application of rituximab; the situation remained similar in the first and last evaluations.

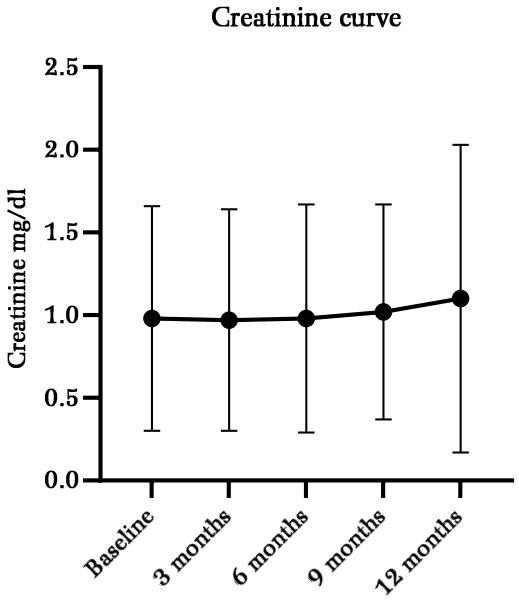

Figure 1. Serum creatinine curve

Proteinuria

Proteinuria presents significantly lower values from the rituximab supply. From the third month, significant changes are observed that are maintained at six, nine, and twelve months. Therefore, rituximab has had an impact mainly on reducing the level of proteinuria. It was observed that initially, prior to the use of rituximab, there were 26 patients with proteinuria; in the subsequent quarterly assessment, a gradual decrease in proteinuria over 24 hours was evident. The evolution is notorious; the number of patients over 12 months varies from 2 to 10, with decreased proteinuria revealing significant changes after using rituximab (Table 2 and Figure 3).

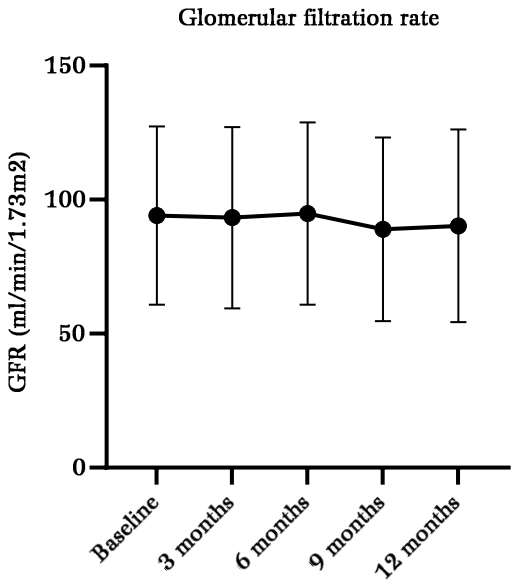

Figure 2. Glomerular filtration rate in the study group.

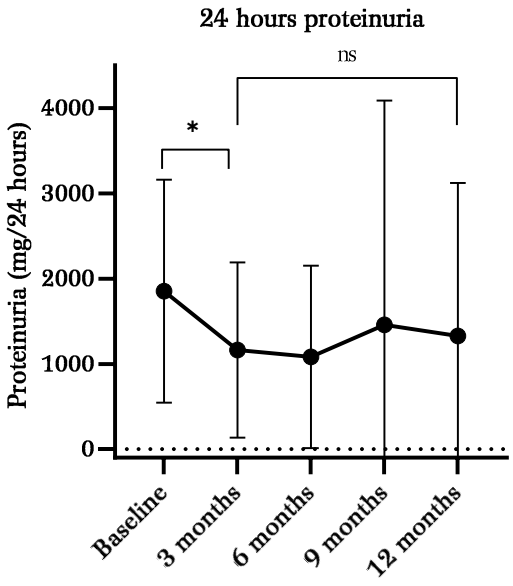

Figure 3Proteinuria in 24-hour urine.

Table 2. 24-hour urine proteinuria in the study group.

	No.	Average	Standard deviation	z	Sig. Asymptotic (bilateral)
Basal	28	1853.18	1307.78	-	-
3 months	28	1163.95	1026.65	-3,643	<0.0001
6 months	28	1082.88	1068.97	-3,051	0.002
12 months	28	1459.02	2629.29	-2,869	0.004

Discussion

A large and highly varied proportion of patients with systemic lupus erythematosus are affected by any form of lupus nephritis from 25% to 75% of the cases, of which 5-20% develop chronic kidney disease, which represents a significant risk factor for morbidity and mortality [4].

In this study, 28 patients with lupus nephropathy who used rituximab were registered and treated in 2018 at José Carrasco Arteaga Specialty Hospital, in which 42.85% of the patients were between 40 and 49 years old, similar to a study carried out by Mieles at the Abel Gilbert Pontón Hospital in the city of Guayaquil, where the age between 45 and 54 years was more frequent [5].

The incidence and prevalence rates for the presentation of SLE are much more frequent among women than among men, with a 10:1 ratio. In Spain, the Rheumatology Society, in its observational study, demonstrated a higher prevalence of women with lupus nephritis at 85.7%; in this study, the prevalence in women was 78.6%, the same as a study carried out in Quito in which the prevalence was 85.9% in women [3].

The histological type of lupus nephritis is closely related to the prognosis of lupus nephritis, so it is essential to perform a renal biopsy in all patients with SLE [6, 7]. In this study, patients with type V LN were the most prevalent at 35.7%. On the other hand, by protocol, 48.7% of patients admitted to biological treatment in Spain [3] corresponded to type IV, and only 10.3% corresponded to type V. This difference in the type of lupus nephritis is given by the size of the sample, by the period studied and by the inclusion protocol in each of the hospitals [8].

Regarding the main results in a study carried out by the Pérez Santana group [4] at the Central Hospital "Dr. Ignacio Morones Prieto" in Mexico, 50 NL patients were included. It was determined that after the sixth month of rituximab use, serum creatinine values decreased significantly from an average value of 1.25 mg/dl to 1.01 mg/dl, showing improvement in renal function. In this study, the creatinine measurement did not show a significant elevation or decrease, and the glomerular filtration rate was maintained.

In their study, Zhong et al. [9] determined the use of rituximab as a promising therapy for treating LN due to its significant clinical efficacy and favorable safety profile. In their results, the

use of the drug significantly reduced proteinuria values in addition to the organic damage, showing a mean difference of -2.79 and a *P value* <0.01, similar results to the present study, where the mean difference was -2.938 and a *P value* <0.003, suggesting that rituximab therapy can prevent the development of kidney damage, at least in the short term.

Chavarot et. to the. [8] showed that 13 of 15 patients (87%) enrolled in their study experienced remission of severe proteinuria in a median time of 5 months in the absence of serious adverse events, resulting in long-term remission of proteinuria and an excellent tolerance profile. However, to a lesser extent, in this study, only 10 of the 28 patients presented a decrease in proteinuria, evidenced by a previous mean of 1853.18 mg in 24 hours and proteinuria after 12 months of 1328.29 mg in 24 hours. In contrast, Alshaiki et al. [6], in a meta-analysis, showed that proteinuria decreased insignificantly in patients with lupus nephritis, with a mean difference of -2.52 Conversely, the patients in our study showed a significant variation in proteinuria with a different mean of -2.938, $P = 0.003$, with a significant variation prior to the use of biologic therapy with rituximab.

Diaz et al. [7] mentioned that rituximab might be an effective option for patients with lupus nephritis, especially in those who do not respond to standard treatment or who experience a new flare after immunosuppressive treatment. He observed that the proteinuria values decreased (P <0.001) at 12 months, a similar value and in agreement with this study that allows us to demonstrate the efficacy of rituximab in the short term with the decrease in proteinuria.

Conclusions

Rituximab shows nonsignificant differences in plasma clearance and creatinine but not in the 24-hour proteinuria values; the difference is significant, demonstrating in our study that the use of rituximab serves as a stabilizer without disease progression and with proteinuria improvement. The most common lupus glomerulopathy in our environment was membranous nephritis, with a prevalence of 35.7%. The sex with the highest prevalence in this study corresponded to women, with a 78.6% prevalence compared to 21.4% of men. The age group with the highest percentage is located in the age range of 40 to 49 years; the average age was 38.36, the minimum age was 21, and the maximum was 67.

Abbreviations

SLE: systemic lupus erythematosus.
LN: lupus nephropathy.
GFR: glomerular filtration rate.

Supplementary information

Supplementary materials have not been declared.

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Does not apply.

Author contributions

Miriam Gabriela Méndez Quizhpi: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.
Alex Andrés Betancourt Maldonado: conceptualization, supervision, validation, visualization, and writing: review and edition.
Sonia Catalina Rivera González: Methodology, validation, supervision, writing: Review and editing.
All authors read and approved the final version of the manuscript.

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The authors provided the costs of the research.

Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable scholarly request.

Statements

Ethics committee approval and consent to participate

The Bioethics committee approved this study for research in human beings of the Faculty of Medical Sciences of the University of Cuenca.

Consent for publication

It does not apply when images or photographs of the physical examination or X-rays/CT/MRI of patients are not published.

Conflicts of interest

The authors report having no conflicts of interest.

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