



Evaluation of remission of lupus nephritis in patients aged 18 to 45 years with induction immunosuppressive treatment. A single-center observational study.

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Abstract

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Introduction: Lupus nephritis (LN) occurs in 50% of patients with systemic lupus erythematosus (SLE). The standard of induction treatment consists of corticosteroids plus immunosuppressants such as cyclophosphamide or mycophenolate mofetil (MMF). Achieving remission correlates with long-term renal survival. The objective of the present study was to evaluate the remission of LN in patients aged 18 to 45 years with induction immunosuppressive treatment to assess the effectiveness of cyclophosphamide and MMF.

Methods: A retrospective analytical observational cohort study was conducted at the Eugenio Espejo Specialty Hospital. There were 185 patients with LN, 68 of whom met the inclusion criteria. The selected variables were sex, ethnicity, age at diagnosis of lupus and LN, antiphospholipid syndrome (APS) antibodies, SLEDAI-2K, HBP, ISN/RPS Class, induction immunosuppressant, clinical remission and reactivation. Descriptive tests were performed, and inferential tests with a P value <0.05 in the SPSS version 25 program were conducted.

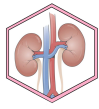
Results: Sixty-eight patients were analyzed. LN was more frequent in women (95.6%) of mixed ethnicity (97.1%), with a mean age of diagnosis of lupus of 27.7 ± 8.1 years and of LN of $28.8 \text{ years} \pm 9.3$ years; 16.2% presented positive antibodies for APS, and 63.2% presented HTN at diagnosis. According to renal biopsy, most patients were classified as LN class IV. At 3.6 and 12 months, no difference was found in remission or reactivation between the cyclophosphamide and MMF groups ($P < 0.05$).

Conclusion: The efficacy of MMF is comparable to that of cyclophosphamide in terms of remission and reactivation in our population.

Keywords:

Immunosuppressive therapy, Lupus nephritis, Remission, Reactivation.

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Systemic lupus erythematosus (SLE) is a chronic, multisystemic and complex autoimmune disease with significant variability in its clinical presentation, evolutionary course and prognosis [1]. The epidemiology of SLE reveals marked global variability, and it is considered a rare disease [2].

Among the various manifestations of SLE, Lupus Nephropathy (LN) is a critical and challenging complication that occurs in approximately half of SLE patients. Anomalies in innate and adaptive immunity and genetic polymorphisms predispose certain ethnic groups to this pathology and are more common in Latin Americans, African Americans, and Asians [3-5].

The alterations in the urinary sediment observed in the elemental and microscopic urine of a patient with SLE led us to think about a possible association with LN; however, histopathological studies remain the gold standard for its diagnosis [6].

Its treatment and prognosis constantly evolve as new therapies and therapeutic approaches emerge. Despite this, there are no studies in Ecuador in patients with LN that assess the efficacy of two of the drugs most commonly used as part of induction treatment worldwide and that are included in the National Table of Basic Medicines of Ecuador, Cyclophosphamide and mycophenolate [7].

SLE is considered a global health problem, with a prevalence that ranges between 13.0 and 7713.5 per 100,000 inhabitants per year and an incidence between 1.5 and 11.0 per 100,000 inhabitants per year [8,9].

LN is one of the most frequent complications that unevenly affects certain ethnic groups, with a higher incidence in African American (34%-51%), Hispanic (31%-43%), and Asian (33%-55%) patients. Compared to Caucasian patients (14%-23%) [3,10].

LN leads to an increase in the absolute risk of progression to chronic kidney disease (CKD) and increases the probability of death at ten years of evolution from 6 to 6.8 times more than in patients with SLE without nephritis, which forces us to identify this condition early and administer timely immunosuppressive treatment [3].

After establishing the histopathological diagnosis of lupus nephritis, treatment is based mainly on the use of glucocorticoids plus immunosuppressants [11]; two of the essential immunosuppressants used in induction therapy, cyclophosphamide and MMF, are included in the present work.

The therapeutic results can vary significantly according to the inherent conditions of the patients, such as ethnicity, tolerance to the drug, and adverse effects. However, it has yet to be possible to determine a difference concerning the efficacy between cyclophosphamide and MMF [12,13].

When reviewing the studies carried out in the national context based on Pubmed, Scielo, Epistemonikos, and Web of Science, we found 29 studies on LN, of which only 2 included induction treatments; however, biological drugs such as Rituximab were not identified, and cohort studies or clinical trials involving Cyclophosphamide or MMF were not found. In addition, based on COBUEC repositories, approximately 82 studies related to LN were found, all of which covered the epidemiological aspects of LN prevalence and mortality

but not aspects associated with the therapeutic efficacy of induction schemes and their relationship with clinical remission.

Faced with this situation, this study provides information on our population regarding therapeutic efficacy in clinical remission with two drugs recommended by international and national guidelines [7,11].

The objective of this research was to evaluate the frequency of remission of lupus nephritis in patients aged 18 to 45 years who received immunosuppressive induction therapy for the evaluation of the efficacy of cyclophosphamide and MMF at the Eugenio Espejo Specialty Hospital, Pichincha- Ecuador, during the period from 2018-2022.

Materials and methods

Study design

An observational, analytical, and retrospective study was carried out.

Stage

This research was conducted at the Eugenio Espejo Specialty Hospital, Pichincha-Ecuador, from January 1, 2018, to December 31, 2022.

Universe and sample

The population consisted of 185 records of patients diagnosed with LN between 2018 and 2022 at the Eugenio Espejo Specialty Hospital, of which 68 patients met the inclusion criteria. The sample size was not estimated due to the anonymized database access of the entire population.

Inclusion criteria

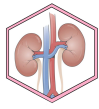
Patients aged 18 to 45 years with a confirmed histopathological diagnosis of LN and referred for immunosuppressive treatment, who completed the follow-up periods considered in the induction phase of the immunosuppressive treatment and whose clinical parameters were available, were included. Activity criteria for lupus nephritis.

Exclusion criteria

- Patients with a glomerular filtration rate lower than 30 mL/min/1.73 m² at admission.
- Patients whose comorbidities have not allowed the administration of the induction regimen with immunosuppressants.
- Pregnant or lactating patients at the time of admission.
- Patients whose records did not have complete clinical or follow-up information for the execution of this research.

Variables

The variables studied were sex, ethnicity, age at diagnosis of SLE and LN, APS antibodies, SLEDAI-2K, HTN, ISN/RPS class, induction immunosuppressant, clinical remission, and reactivation, detailed in the operationalization table of variables a continuation.



Statistical analysis

The qualitative variables were described through relative and absolute frequencies. In contrast, the quantitative variables were analyzed with measures of central tendency (mean/median) and dispersion (standard deviation, range, maximum and minimum value). The results of these analyses are presented in tables or representative graphs.

Bivariate analysis

To establish the relationship between the sociodemographic and clinical variables related to the severity of the disease and the occurrence of remission in the follow-up periods, the chi-square test of Pearson's test of hypothesis contrast for qualitative variables was applied. An α value of 1.96 was established with a $P < 0.05$ for statistical significance with a 95% confidence interval. Additionally, the Pearson chi-square test was used to analyze the relationship between the type of drug used for the induction of clinical remission and the reactivation or relapse of the disease during the follow-up period. A $P < 0.05$ was considered to indicate statistical significance.

Results

Study participants

Sixty-eight patients were included in the study.

Characteristics of the study group

There were 65 women (95.6%) with a Mestizo ethnicity in 97.1% of the patients ($n = 66$). Regarding their clinical history, 20.6% ($n = 14$) had a previous diagnosis of SLE, 14.7% ($n = 10$) of those who were taking MMF plus corticosteroids, 4.4% ($n = 3$) were taking corticosteroids alone, and 1.5% ($n = 1$) were taking azathioprine. A total of 16.2% of patients ($n = 11$) were diagnosed with APS with positive antibodies. The mean age at diagnosis of SLE was 27.7 ± 8.1 years, and that at diagnosis of LN was 28.8 ± 9.3 years. Among the patients with a previous diagnosis of SLE, the mean age at presentation of LN was 4.8 ± 2.2 years (Table 1).

Characteristics of the group with signs of severity

Table 2 shows that 100% of patients ($n = 68$) presented with active SLE with a 2K SLEDAI > 12 (94.1%). The most frequent extrarenal manifestations were inflammatory rash in 19.1% ($n = 13$), arthritis in 13.2% ($n = 9$), and alopecia in 5.9% ($n = 4$). Regarding the analytical parameters of the SLEDAI-2K, 5.9% ($n = 4$) presented with leukopenia, 11.8% ($n = 8$) with platelet deficiency, 70.6% ($n = 48$) with the consumption of complement C3, 76.5% ($n = 52$) with the consumption of C4 and 19.1% ($n = 13$) with high levels of anti-DNA. Regarding the SLEDAI 2K and the renal domain, 25% ($n = 17$) reported urinary casts, 88.2% ($n = 60$) reported microhematuria, 77.9% ($n = 73$) reported pyuria, 39.7% of patients ($n = 27$) had proteinuria between 500 and 3500 mg, and 60.3% ($n = 41$) had proteinuria greater than 3500 mg, with a mean of 3030 ± 2070 mg in 24-hour urine.

Table 1. Sociodemographic and clinical characterization.

Variable		"n" = 68	%
Sex	Female	65	95.6
	Male	3	4.4
Ethnicity	Mixed race	66	97.1
	Afro-Ecuadorian	2	2.9
Clinical history	High blood pressure	10	14.7
	Recurrent urinary tract infection	3	4.4
	Systemic Lupus Erythematosus	14	20.6
	Other	16	23.5
Previous medication	None	25	36.8
	Azathioprine	1	1.5
	Corticoid	3	4.4
	MMF + corticosteroid	10	14.7
SAF	Yes	53	77.9
	No	11	16.2
		mean (years) \pm SD	
Age	SLE diagnosis,	27.7 ± 8.1	
	Diagnosis of LN,	28.8 ± 9.3	
	SLE/NL age difference *	4.8 ± 2.2	

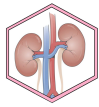
* Patients with a history of SLE.

In addition, other clinical and analytical parameters at admission independent of the SLEDAI 2K were described; 63.2% of patients ($n = 43$) presented high blood pressure at diagnosis. A mean creatinine of 1.06 ± 0.56 mg/dl was observed for the nitrogen compounds. A total of 64.7% of patients ($n = 44$) were admitted with a creatinine concentration < 1.2 mg/dl, and only 11.8% ($n = 8$) had a creatinine concentration > 2 mg/dl, as described previously (Table 2).

Classification by renal biopsy

Regarding renal biopsy, the most frequently biopsied classes were 44.1% ($n = 30$) Class IV LN, 23.5% ($n = 16$) Class III, and 11.8% ($n = 8$) Class II (Table 3).

Table 4 When comparing the clinical and analytical characteristics with the renal biopsy, the proliferative classes presented a greater frequency of arterial hypertension: Class III, 73.3% ($n = 22$); Class IV, 75% ($n = 12$); and mixed Classes III/IV + V, 71.42% ($n = 5$). Regarding active urinary sediment, microhematuria occurs in $\geq 80\%$ of patients in Classes II, III, IV, and III/IV + V; pyuria occurs more frequently in Classes III/IV + V and Class II in 100% of patients. A proteinuria > 3500 mg/24 hours was more frequent in Classes III/IV + V and V in 57.14% of patients. Regarding serology, there was greater consumption of complement in the proliferative classes. In class III, 81.25% ($n = 13$) consumed C4, and 76.6% ($n = 23$) of patients in class IV consumed C3 and C4. High levels of Anti-dDNA were detected with a frequency $> 80\%$ in Class III, Class III/IV + V, and Class II ($P > 0.05$).

**Table 2 .** Clinical and analytical characterization.

Variable		"n"=68	%
SLEDAI 2K	< 3	0	0.0
	3 a 12	4	5.9
	> 12	64	94.1
Extrarenal manifestations	Alopecia	4	5.9
	Arthritis	9	13.2
	Inflammatory rash	13	19.1
	Other	30	44.1
	None	12	17.6
Leukocytes	Leucopenia <3000	4	5.9
	Normal	53	77.9
	Leucocytosis > 1100	11	16.2
Platelets	< 100,000	8	11.8
	Normal	60	88.2
Complement C3	Low	48	70.6
	Normal	20	29.4
Complement C4	Low	52	76.5
	Normal	16	23.5
Anti DNA	Elevated	55	80.9
	Normal	13	19.1
Urinary cylinders		17	25.0
Proteinuria in 24 hours	0.5–3.5 g/24 horas	27	39.7
	>3.5 g/24 horas	41	60.3
Microhematuria		60	88.2
Piuria		53	77.9
HT	<1.2 mg/dl	44	64.7
	1.2 a 2 mg/dl	16	23.5
	> 2 mg/dl	8	11.8

HT: arterial hypertension.

Table 3. Classification by biopsy.

Class	"n" = 68	%
II	8	11.8
III	16	23.5
III/IV + V	7	10.3
IV	30	44.1
V	7	10.3

Induction treatment

A total of 45.6% of patients ("n" = 31) received intravenous cyclophosphamide as induction treatment, which was comparable to the 45.6% of patients ("n" = 31) who received MMF; 8.5% ("n" = 6) received combined treatment, as detailed in [Table 5](#).

Among the 31 patients who received intravenous cyclophosphamide as induction treatment, only 43.5% ("n" = 27) maintained maintenance therapy with MMF for 12 months, and 6.5% ("n" = 4) rotated immunosuppressive treatment. Regarding MMF, 37.1% ("n" = 23) of patients maintained follow-up for 12 months, and 12.9% ("n" = 8) rotated the immunosuppressant ([Table 6](#)).

Frequencies of clinical remission at 3, 6, and 12 months

The follow-up group during the study period consisted of 27 patients who received induction treatment with cyclophosphamide and 23 who received MMF. At three months, the absence of remission and partial remission were comparable between the patients who received induction treatment with cyclophosphamide and those who received MMF. Regarding complete remission, 22.2% ("n" = 6) of the patients were in the cyclophosphamide group, and 8.7% ("n" = 2) were in the MMF group; however, these findings were not statistically significant ($P = 0.42$). Among the 25 patients who received cyclophosphamide as induction therapy, 20% ("n" = 5) did not achieve remission, 40% ("n" = 10) achieved partial remission, and the other 40% ("n" = 10) achieved complete remission. Among the 21 patients who received MMF, 13% ("n" = 3) did not remit, 47.8% ("n" = 11) achieved partial remission, and 30.4% ("n" = 7) achieved complete remission. However, according to the statistical analysis, there was no difference between remission at six months and the type of drug received ($P = 0.69$). At 12 months, 40 patients achieved partial or complete remission. Of the 21 patients who received cyclophosphamide as induction therapy, 42.9% (n = 9) achieved partial remission, and the other 57.1% (n = 12) achieved complete remission. Among the 19 patients who received MMF, 36.8% ("n" = 7) were partially remitted, and 63.2% ("n" = 12) were wholly remitted. However, there was no relationship between remission at 12 months and the type of drug received ($P = 0.69$). It is detailed in [Figure 1](#) and [Figure 2](#).

[Figure 2](#), at six months, the reactivation frequency for patients who received cyclophosphamide was 7.4% ("n" = 2), and for those who received MMF, it was 8.7% ("n" = 2). At 12 months, these frequencies were 22.2% ("n" = 6) in the cyclophosphamide group and 17.4% ("n" = 4) in the MMF group; however, there were no statistically significant differences at six months ($P = 0.89$) or at 12 months ($P = 0.67$).

Variation in proteinuria and creatinine at 3, 6, and 12 months

[Figure 3](#), patients who received cyclophosphamide had a mean proteinuria of 3500 mg/24 hours at the start of induction treatment, unlike those who received MMF, who had a mean proteinuria of 2500 mg/24 hours ($P = 0.06$). At six months, the cyclophosphamide group presented a <50% reduction concerning the initial proteinuria, unlike the MMF group, which offered a 50% reduction ($P = 0.01$). At 12 months, only the MMF group achieved a reduction of <1 gram/24 hours ($P = 0.01$).

[Figure 4](#), creatinine levels at the start of induction treatment were more significant in the cyclophosphamide group, with a mean of 1.29 ± 0.6 mg/dl, than in the MMF group, with a mean of 0.81 ± 0.3 mg/dl ($P = 0.001$). In the cyclophosphamide group, the creatinine trend at 3, 6, and 12 months was downward; in the mycophenolate mofetil group, at three months, creatinine increased slightly, with a subsequent decrease at six months and stabilization at 12 months.

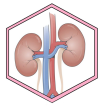


Table 4. Clinical and analytical characterization according to renal biopsy.

Variables	Proliferative classes			Nonproliferative classes		P value
	Class III "n"= 16	Class III/IV + V "n"= 7	Class IV "n"= 30	Class II "n"= 8	Class V "n"= 7	
-Woman	16 (100)	7 (100)	28 (93.33)	8 (100)	6 (85.71)	0.49
Age (Years)	27.8 ± 9.5	27.2±8.7	26.8 ± 8.3	29.6 ± 8.2	2.5± 7.9	0.11
Age of diagnosis of LN	29.8±10.3	28.0±8.1	27.4±8.2	29.8 ± 8.1	30.4±9.9	0.15
HTN "n", (%)	12 (75)	5 (71.42)	22 (73.33)	5 (62.5)	2 (28.57)	0.20
Creatinine <1.2 mg/dl	11 (68.75)	6 (85.71)	15 (50)	7 (87.5)	(71.42)	
Creatinina 1.2-2 mg/dl	3 (18.75)	1 (14.27)	10 (33.33)	0 (0)	2 (28.57)	0.42
Creatinine > 2 mg/dl	2 (12.5)	0 (0)	5 (16.66)	1 (12.5)	0 (0)	
Mean ± SD	0.8 ± 0.5	1.1 ± 0.5	0.9 ± 0.4	1.2 ± 0.5	0.7 ± 0.3	
Proteinuria 0.5-3.5 g/24 h	11 (68.75)	3 (42.85)	19 (63.33)	7 (87.5)	3 (42.85)	
Proteinuria >3.5 g/24 horas	5 (31.25)	4 (57.14)	11 (36.66)	1 (12.5)	4 (57.14)	0.31
Mean ± SD	2.990 ± 1.080	3.01 ± 2.20	3.031 ± 2.02	3.150 ± 2.863	3.001± 2.05	
Microhematuria	13 (81.25)	7 (100)	24 (80)	7 (87.5)	5 (71.42)	0.67
Piuria "n", (%)	11 (68.75)	7 (100)	24 (80)	8 (100)	4 (57.14)	0.12
C3 Low	10 (62.50)	5 (71.42)	23 (76.66)	5 (62.5)	5 (71.42)	0.86
C3 Normal	6 (37.50)	2 (28.57)	7 (23.33)	3 (37.5)	2 (28.57)	
C4 Low	13 (81.25)	6 (85.71)	23 (76.66)	6 (75)	5 (71.42)	
C4 Normal	3 (18.75)	1 (14.27)	7 (23.33)	2 (25)	2 (28.57)	
High antiDNA	13 (81.25)	7 (100)	23 (76.66)	7 (87.5)	5 (71.42)	0.62
Normal AntiFNA	3 (81.25)	0 (0)	7 (23.33)	1 (12.5)	2 (28.57)	0.62
SLEDAI 2 K: 3-12	2 (12.5)	0 (0)	0 (0)	0(0)	1 (14.28)	0.18
SELEDAI 2 K:>12	14 (87.5)	7 (100)	30 (100)	8 (100)	6 (85.71)	

DE: Standard Deviation.

Table 5. Induction treatment.

Treatment type	"n"=68	%
Cyclophosphamide	31	45.6
Mycophenolate mofetil	31	45.6
They start with Cyclophosphamide but rotate to Mycophenolate mofetil	5	7.4
Start with Mycophenolate mofetil and rotate to Cyclophosphamide	1	1.1

Table 6. Rotation of medications.

	Treatment	"N" = 62	%
Cyclophosphamide	Follow-up for 12 months	27	43.5
	Rotation : At 3.1 months: 2 to Rituximab and 2 to plasma exchange	4	6.5
Mycophenolate mofetil.	Follow-up for 12 months	23	37.1
	Rotation : -At 3.1 months: 4 to Cyclophosphamide; -At 6 months: 3 to Cyclophosphamide and 1 to plasma exchange	8	12.9

Table 7 . Relationship between sociodemographic and clinical variables with the frequency of clinical remission and reactivation of lupus nephritis at 12 months.

Variables	Referral		Reactivation		P value	
	n: 40	%	n:10	%		
Sex	Female	40	100	10	100	Not calculable
	Mixed race	39	97.5	10	100	
Ethnicity	Afro-Ecuadorian	1	2.5	0	0	0.61
SAF		6	15	3	30	0.26
SLEDAI 2K	< 3	0	0	0	0	0.79
	3 to 12	3	7.5	1	10	
	> 12	37	92.5	9	90	

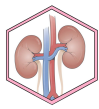


Figure 1. Frequencies of referral at 3, 6, and 12 months.

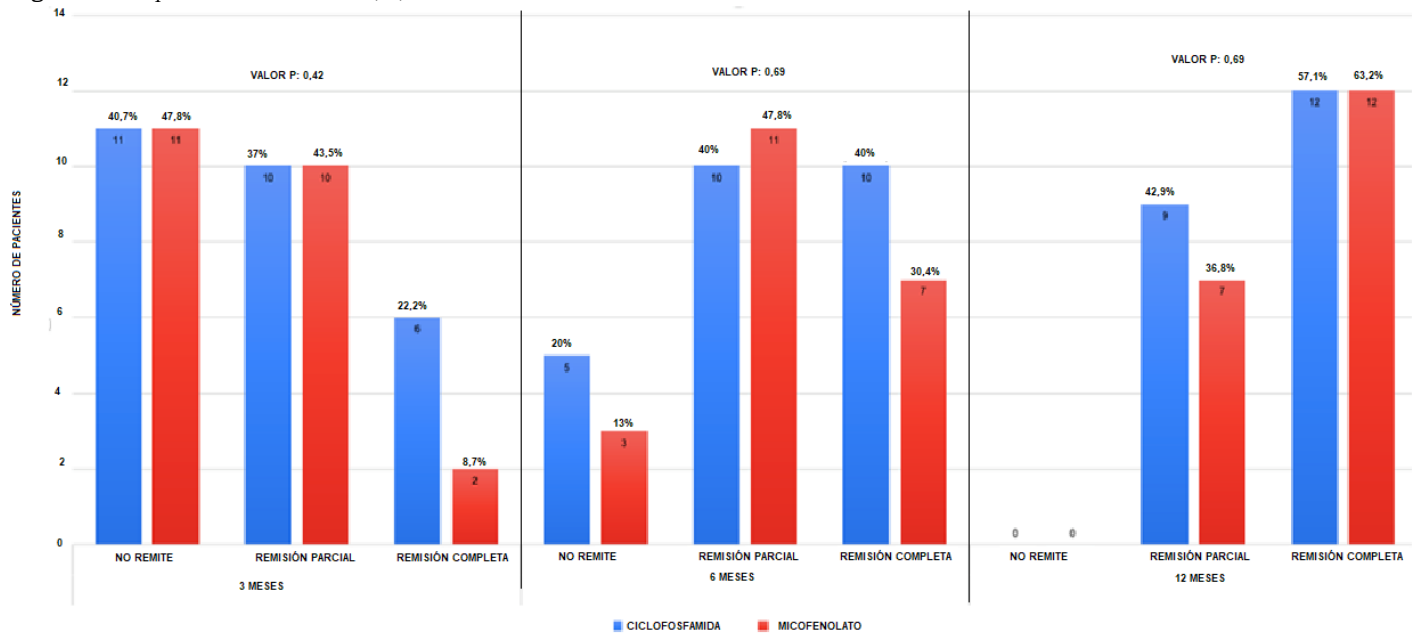
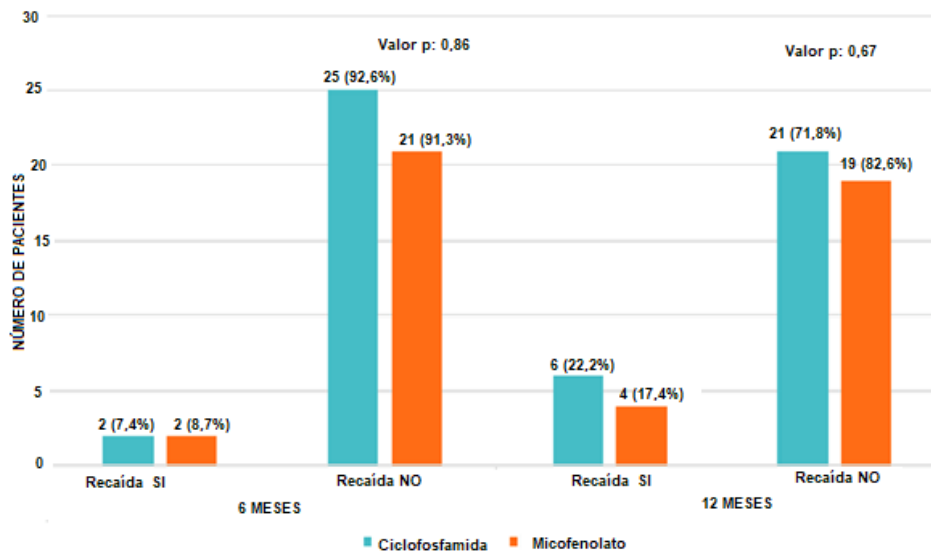


Figure 2. Reactivation frequencies at 6 and 12 months.



Relationships between sociodemographic and clinical variables and remission and reactivation

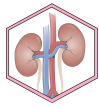
The variables ethnicity, antiphospholipid syndrome status, systemic lupus erythematosus status, and SLEDAI 2K score were not related to remission or reactivation at 12 months ($P \Rightarrow 0.05$); the P value of the sex variable could not be estimated. It is striking that patients with a history of SLE maintain reactivation frequencies similar to those without such a history (Table 7).

Patients who had lower 24-hour proteinuria in the urine ($x = 1459$) presented more significant complete remission at 12 months; in

contrast, patients with a higher 24-hour urine proteinuria at admission ($x = 2921.5$) presented greater reactivation, and these differences were statistically significant ($P = 0.02$) (Figure 5).

Discussion

In this study, the population was characterized by a large percentage of women (95.6%). These findings are consistent with those of studies in India and Egypt, which reported a 92 to 96.7% prevalence in women [14,15].



About ethnicity in this study, 97.1% of patients were self-determined to be Hispanic, and 2.9% were self-determined to be Afro-Ecuadorian, without having a white or indigenous population. Previous reports indicate that LN is more frequent in African American, Latin-American, and Asian patients [3]. According to local studies [16], 82.6% of Hispanics, 8% of Afro-Ecuadorians, 8% of whites, and only 2% are Indigenous. This difference can be explained by ethnicity, a subjective perception of the person, and most of the patients in the study were Hispanic.

The mean age at which patients presented with SLE was 27.7 ± 8.1 years, and the average age at which patients were diagnosed with LN was 28.8 ± 9.3 years; similar data on the age at presentation have been reported in other studies [17,18].

Patients with LN are generally expected to develop disease within the first five years after the diagnosis of SLE [19]. In the present study, the difference was one year, and in patients with a history of SLE, the difference was 4.8 years. These reports of NL of short development have been reported in Colombia [20], related to the late diagnosis of SLE.

Approximately 20 to 40% of patients with SLE are positive for antiphospholipid antibodies [21]. In the present population, 16.2% of patients presented positive antibodies without associated symptoms at the time of LN diagnosis. This difference, less than that reported, could be related to the fact that only patients who presented positive antiphospholipid antibodies at the time of diagnosis of LN were considered.

To extrarenal manifestations, 82.3% of the population in this study presented some clinical symptoms. Among the most frequent extrarenal manifestations were inflammatory rash (13%), arthritis (9%), and alopecia (4%). These findings are consistent with those reported by Bartaula et al. [22]. Among the 92 patients studied, 80.4% presented some associated clinical manifestations, 41.3% presented polyarthritis, and 17.4% presented malar rash. Additionally, in the 45 patients in the study by Gururani et al. [17], 39% presented mucocutaneous manifestations, and 33% presented musculoskeletal manifestations. The two main external manifestations of our population are those described in the literature.

Regarding the SLEDAI 2K score, 100% of the patients presented with SLE activation at the beginning of the study, with scores ranging from 3 to 12 in 5.9% and > 12 in 94.1% of the patients; these findings are similar to those of previous studies [17] in which 100% of the patients presented with disease activation with an SLEDAI score of 12 ± 4 . Regarding the renal domain, in this study, most patients presented active sediment, with 60 patients with microhematuria and 53 patients with pyuria; these statistics are related to those reported by Islam et al. [23].

Figure 3. Variation in 24-hour urine proteinuria at 3, 6, and 12

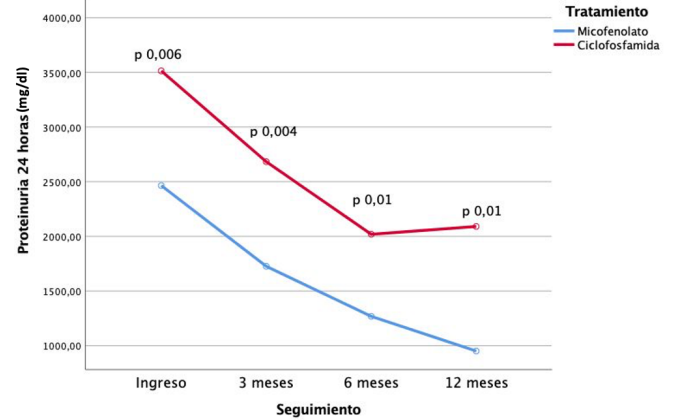


Figure 4. Creatinine variation at 3, 6, and 12 months according to the induction immunosuppressive treatment.

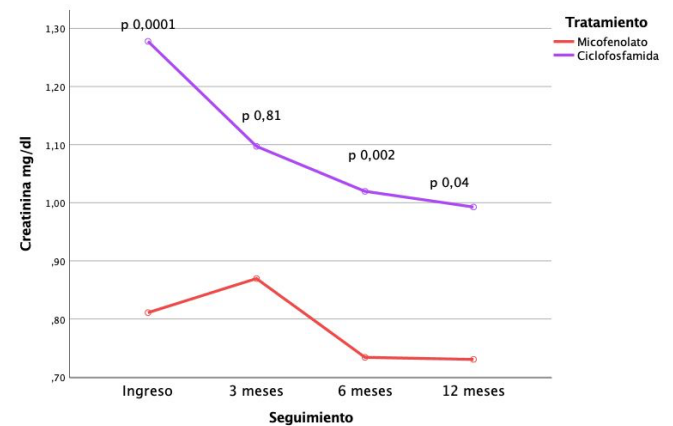
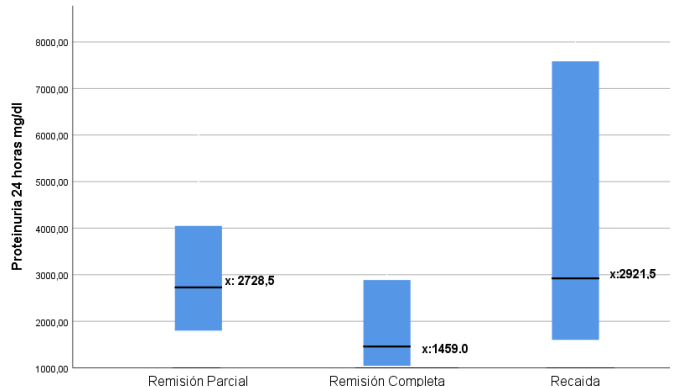
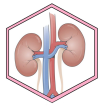


Figure 5. Relationship of initial proteinuria with remission and reactivation at 12 months.



As indicated by the SLEDAI-2K score and renal domain, serology is associated with complement consumption and increased anti-DNA. In this study, most patients consumed 70.6% C3 and 76.4% C4 supplements. Regarding the increase in anti-DNA, it was present in 80.9% of this population; these data are comparable to those of a Colombian study [24] in which 64% of 131 Colombian



patients consumed C3, and 73% increased anti-DNA. The present data are similar to those described in the literature, in which patients with SLE reactivation presented active urinary sediment, complement consumption, and increased anti-DNA.

To other clinical parameters, 63.2% of the population presented arterial hypertension, which differs from several studies in which the prevalence was 20 to 31% [17,23 24]. This difference may be related to genetic factors and the noninclusion of volume-dependent hypertensive patients.

Histopathological analysis revealed that the most frequently biopsied LN type was proliferative. Thus, Class IV or diffuse LN was present in 44.1% of patients, and Class III or focal LN was present in 23.5% of patients; these findings resemble those reported by Gasparotto et al. [25], in which Class IV LN represented 50% of patients and Class III 25%. In the study by Vivek et al. [26], the classes of LN most frequently biopsied were Class IV, followed by Class III. In addition, an increase in mixed forms has been reported over the years. In the present study, 10.3% of biopsies were reported with Class III/IV + V LN, a finding that reflects the updating process of the ISN-RPS classification. These data are consistent with what was reported in the study by Restrepo et al. [27], in which 41.2% of 34 Colombian patients presented Class IV LN, and mixed forms were present in 14.8%.

Regarding the clinical characteristics according to the type of renal biopsy, most patients were female. Overall, 100% of women were in Class III and III/IV + V, 93.3% were in Class IV, and 85.7% were in Class V. This higher frequency in females agrees with the findings of previous studies [28]. Regarding the age of presentation of LN, in this study, Class V had a mean age of 30.4 ± 9.9 years, which differs from that described by Islam et al. [23], in which the mean age of presentation was 45.12 ± 13.6 years; this difference was due to the non-inclusion of the population older than 45 years.

When comparing the clinical and analytical characteristics of the proliferative and nonproliferative classes of the renal biopsy, in the present study, patients with proliferative LN presented a greater frequency of HTN, which was described in more than 70% of patients. About active urinary sediment, all the biopsied classes presented microhematuria and pyuria; these findings were more frequent in Class III/IV + V in 100% of patients, proteinuria > 3500 mg/24 hours was more frequent in Class V in 57.14%, and in Class III/IV + V. To arterial hypertension, the present finding resembles that described by Gopal et al. [14], in which patients with Class III/IV LN had a significantly greater frequency of hypertension in 52.1%. In addition, in this Indu population of 333 patients, active urinary sediment was detected in all biopsied Classes and was more frequent in proliferative Classes III, IV, and III/IV + V. Similarly, in a study by Islam et al. [23] involving 104 patients from Asia, microhematuria was reported in all biopsied Classes and was more frequent in Classes VI and IV. This discrepancy between studies could be associated with the numerical difference between patients included in each biopsy class. Gopal et al. [14] also showed that proteinuria > 3 grams is more frequent in

Class V or membranous LNs, findings that are consistent with the present study.

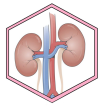
For serology and its histopathological relationship, in the present study, the proliferative and nonproliferative classes presented an increase in AntiDNA in 81% and 80%, respectively, consistent with those described by Gopal et al. [14]. Compared with the complement class, the proliferative class IV class presented greater consumption of C3 in 76.66%, and the class III, III/IV+V class showed greater consumption of C4 in 81.25% and 85.71%, respectively. These findings are similar to those reported by Duran et al. [29], in which the proliferative classes presented greater complement consumption in 88.8% of patients.

When comparing remission between the cyclophosphamide group and the MMF group in our population at 3, 6, and 12 months, it was evident that there was no statistically significant difference in the frequencies of partial remission, complete remission, or no remission between the two groups throughout the period. Similarly, the frequencies of reactivation were similar between the groups that received cyclophosphamide and MMF at 6 and 12 months, findings that resemble those of trials in different populations, as described in Hispanics and non-Hispanics [12], Chinese [30], and Egyptians [31].

The three-month findings indicate no statistically significant difference in nonremission between the groups that received cyclophosphamide and MMF, with 40.7% and 47.8%, respectively. These data are similar to those described by Prasad et al. [32] in an Indian population in which nonremission was similar among patients who received induction treatment with cyclophosphamide (29.9%) and patients who received mycophenolate (30.3%). At six months, 80% of the patients achieved remission with cyclophosphamide and 78.2% with MMF. Complete remission was observed in 40% of the patients who received cyclophosphamide and 30.4% of those who received MMF, although this difference was not statistically significant. These findings are comparable to those described by Appel et al. [12] for ALMS, in which 56% of patients were treated with MMF and 53% with cyclophosphamide.

At 12 months, the overall remission rate in the present study was 80%. Morales et al. explained that induction immunosuppression in LN patients has remained practically unchanged, with a probability of achieving complete or partial remission of 60-70% [33]. This difference is probably because, in the present study, patients who rotated from immunosuppressive treatment were excluded due to lack of response during follow-up; if we included these patients, our remission rates would be lower or comparable to those described worldwide.

In the literature, a specific ethnic and regional influence is described in the response to induction immunosuppressive treatment. In the present study, MMF and cyclophosphamide did not affect remission, considering our population, mostly mestizo (97.1%). These remission data are similar to those described in the ALMS post hoc study [13], in which MMF was not superior to cyclophosphamide. However, when comparing population groups, it was reported that Latin American patients had a lower response to cyclophosphamide (32% vs. 60.7%; $P = 0.003$). This finding may be related to genetic



adverse effects. Thus, cyclophosphamide had more adverse effects on Latin American and African American patients than on Caucasian patients. This finding was not reported in the present study because adverse impacts on the population were not assessed.

Regarding the variation of proteinuria, in the present study, only patients who received MMF at six months achieved a 50% reduction for initial proteinuria. At 12 months, the decrease in MMF was only 1 g in 24-hour urine. Previous reports indicate a reduction of proteinuria > 50% at six months is associated with better renal survival. A level of proteinuria <0.7 g/24 h at 12 months is the best predictor of the probability of end-stage CKD in the long run term [6,34]. This leads us to deduce that, of the present group of patients, those who received MMF had better renal survival than those in the cyclophosphamide group; however, long-term follow-up is needed.

Regarding creatinine at admission, the cyclophosphamide group presented higher creatinine levels than the MMF group. At six months, the serum creatinine level in this group decreased from 1.29 ± 0.6 mg/dl to 1 ± 0.5 mg/dl; conversely, in the MMF group, the creatinine level stabilized between 0.70 and 0.80 mg/dl. These findings are consistent with those described by Sedhain et al. [35], in which serum creatinine decreased from 1.73 to 0.96 in the cyclophosphamide group. However, this trend also occurred in the MMF group, with a decrease in creatinine from 1.24 to 0.91 mg/dl. It could be inferred that this reduction in creatinine present in these studies is because the most seriously affected patients received cyclophosphamide.

When analyzing the sociodemographic and clinical variables with the frequencies of remission and reactivation in the present study, the variables ethnicity, APS, and history of SLE were not significantly different, and no other studies were found that compared these variables at 12 months. In terms of sex, 100% of the participants who experienced remission and relapse after one year were women; this differs from the study by Gopal et al., in which 233 patients responded to immunosuppressive treatment, 221 (94.8%) were women and 12 (5.3%) were men. Of the 60 patients who did not respond to immunosuppressive therapy, 48 (80%) were women and 12 (20%) were men ($P < 0.01$). This difference from the present study is because we did not have male patients who completed the research period. It has been reported that LN is more frequent in women of childbearing age and is more severe in men [36]. This finding agrees with what is present in the present study because of the three male patients for whom the investigation began to rotate from immunosuppression in the follow-up period due to the severity of their SLE and lack of response to treatment.

Concerning proteinuria and its relationship with remission and reactivation at 12 months, patients with complete remission presented a lower range of initial proteinuria, with a mean of 1459 mg/24 hours, than patients with reactivation, who presented more significant initial proteinuria, with a mean of 2921.5 mg/24 hours. There were no patients who did not remit at 12 months. Patients who rotated from immunosuppressive treatment and did not comply with the follow-up period were excluded. The present findings are related to those

reported by Koo et al. [37] in a Korean population in which the urinary protein/creatinine ratio was lower in patients who remitted at 12 months (1.90 ± 4.31 g/g) than in those who did not remit (4.30 ± 4.93 g/g), as described in a study of the Indian population [49] in which patients who responded to treatment had a lower urinary protein/creatinine ratio (0.8-267 g/24 hours) than did those who did not respond to treatment (1.18-4.19 g/24 hours). These findings are consistent with the present study in that proteinuria increases the risk of nonremission and relapse or reactivation in the long term.

Among the study's main limitations, it is worth mentioning the absence of all clinical and analytical variables at the beginning of immunosuppressive treatment, as well as the lack of reporting and standardization of kidney biopsies, which shortened the study sample. Another limitation is that, as a descriptive study with a documentary basis, the data were taken from a secondary source.

Conclusion

LN was more common in female patients of mixed ethnicity, with a mean age at diagnosis of SLE of 27.7 ± 8.1 years and a mean age at diagnosis of LN of 28.8 ± 9.3 years. In addition, according to the histological class, the most frequent was Class IV or diffuse LN. There was no difference in the analysis of the variables sex, ethnicity, APS, or history of SLE with remission and reactivation of LN at 12 months; however, proteinuria at the onset of LN was associated with remission and reactivation 12 months after induction treatment. There was no difference in partial or complete remission frequency at 3, 6, or 12 months between the groups that received cyclophosphamide or MMF as induction therapy. There was no difference in the reactivation frequency at 6 and 12 months between patients who received cyclophosphamide or MMF as induction therapy.

Abbreviations

SLE: Systemic lupus erythematosus.

NL: lupus nephropathy.

SAF: Antiphospholipid syndrome.

Supplementary information

The supplementary materials have not been included.

Acknowledgments

Does not apply.

Authors' contributions

María José Cajas Romero: Data curation, Formal analysis, Fund acquisition, Research, Methodology, Project management, Resources, Software, Writing - original draft.

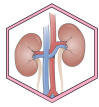
Jorge Chonata Quinteros: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.

All the authors have read and approved the final version of the manuscript.

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The study was self-financed by the authors.

Availability of data or materials



The datasets generated and analyzed during the current study are not publicly available but can be shared with an academic request.

Declarations

Ethics committee approval and consent to participate

This study was approved by the Human Research Ethics Committee of San Francisco de Quito University (CEISH-USFQ). The authors sent the journal editors a copy of the study approval letter.

Consent for publication

Studies that do not publish photographs of patients, CT scans, or X-ray studies are unnecessary.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author information

Does not apply.

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