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Hydroxychloroquine use and blood pressure below 130/80 are associated with remission in lupus nephritis: A cohort study

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ABSTRACT

Introduction: The treatment of lupus nephritis, in addition to immunosuppression, includes the use of adjuvant therapies (antimalarials, statins, blockade of the renin–angiotensin system, and the achievement of blood pressure levels below 130/80). The evidence for the use of these strategies comes from non-autoimmune primary glomerulopathies and there is no information on their impact on the remission of this condition.
Objective: To determine, in patients with lupus nephritis, the use of adjuvant therapies and their association with remission at 12 months.
Materials and methods: A retrospective cohort study was conducted, between 2005 and 2012. Patients who achieved complete remission of nephritis were compared with those who did not. Complete remission was defined by the American College of Rheumatology AdHoc Subcommittee.
Outcomes: Percentage of use of adjuvant therapies. Bivariate and multivariate analysis were performed to define association with remission.
Results: 167 subjects were included (all eligible subjects); 85.6% used antimalarials, 65.5% angiotensin converting enzyme inhibitors, 33.5% angiotensin receptor blockers, 30.7% dual blockade, 29.3% statins, and 85% achieved the goal blood pressure. In the multivariate analysis, the use of hydroxychloroquine (OR = .149; 95% CI: .034–.647; $p = .003$) and the achievement of goal blood pressure (OR = .248; 95% CI: .1–.615; $p = .003$) were associated with remission.
Conclusions: In a cohort of patients with lupus nephritis, the use of hydroxychloroquine and achieving blood pressure values lower than 130/80 were associated with remission at 12 months.

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El uso de hidroxicloroquina y las cifras de presión arterial por debajo de 130/80 se asocian con remisión en nefritis lúpica: un estudio de cohorte

Palabras clave:
Adyuvantes
Farmacéutico
Antimaláricos
Inhibidores de la enzima convertidora de angiotensina
Antagonistas de los receptores de angiotensina
Presión arterial
Lupus eritematoso sistémico
Nefritis

R E S U M E N

Introducción: El tratamiento de la nefritis lúpica, además de la inmunosupresión, comprende el uso de terapias adyuvantes (antimaláricos, estatinas, bloqueo del sistema renina angiotensina y el logro de cifras de presión arterial menores de 130/80). La evidencia del uso de estas estrategias proviene de glomerulopatías primarias no autoinmunes y no hay información de su impacto en la remisión de esta condición.

Objetivos: Determinar, en pacientes con nefritis lúpica, la utilización de terapias adyuvantes y su asociación con remisión a 12 meses.

Materiales y métodos: Se realizó un estudio de cohortes retrospectivo, entre 2005 y 2012. Se compararon los pacientes que lograron remisión completa de la nefritis con aquellos que no lo consiguieron. La remisión completa se definió según el Subcomité AdHoc del American College of Rheumatology.

Desenlaces: Porcentaje de utilización de terapias adyuvantes. Análisis: bivariado y multivariado para definir asociación con remisión.

Resultados: Se incluyeron 167 pacientes (todos los sujetos elegibles). Un 85,6% utilizó antimaláricos, un 65,5% inhibidores de enzima convertidora de angiotensina, 33,5% bloqueadores del receptor de angiotensina, 30,7% bloqueo dual, 29,3% estatinas y en un 85% se logró la meta de presión arterial. En el análisis multivariado, el uso de hidroxicloroquina (OR = 0,149; IC 95%: 0,034-0,647; $p = 0,003$) y el logro de la meta de presión arterial (OR = 0,248; IC 95%: 0,1-0,615; $p = 0,003$) se asociaron a remisión.

Conclusiones: En una cohorte de pacientes con nefritis lúpica, el uso de hidroxicloroquina y lograr cifras de presión arterial menores a 130/80 se asociaron a remisión a 12 meses.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a chronic course and accumulated visceral damage.[1] One of the most frequently affected organs is the kidney, involved in up to 60% of the cases; this is one of the main markers of poor prognosis and mortality in this entity.[2]

The mainstay of treatment in lupus nephritis (LN) is the use of immunosuppressants (cytotoxics between six and 12 months and high doses of glucocorticoids); unfortunately, the short- and long-term response rates to these regimens are less than 40%[3] Given this reality, different management guidelines (European League Against Rheumatism and American College of Rheumatology)[4,5] propose the use of adjuvant therapies such as antimalarials, statins, blockade of the renin–angiotensin–aldosterone system, and the achievement of blood pressure levels lower than 130/80 to diminish intraglomerular pressure, preserve kidney function, prevent disease relapses, and reduce progression to end-stage kidney disease.[5]

The evidence supporting these recommendations is scarce and is extrapolated from non-autoimmune kidney diseases (diabetes mellitus, arterial hypertension, dyslipidemia) and cardiovascular risk management in the general population[6–9] and, until it is known, the frequency of use and the impact that this adjuvant therapy may have in individuals with LN in daily practice is unknown.

The objective of this study was to estimate the frequency of use of adjuvant therapy in LN and determine whether its use has an impact on 12-month remission in a cohort of Latin American mestizo patients in two referral centers.

Materials and methods

Design

An analytical observational study of a retrospective cohort was carried out.

Participants

All patients with SLE older than 14 years of age, classified according to the 1999 modified American College of Rheumatology criteria,[10] with nephritis confirmed by biopsy according to the 2003 classification of the International Society of Nephrology and the Renal Pathology Society[11] attended in the outpatient and inpatient services, between 2005 and 2012, in two university hospitals of high-complexity level in northwestern Colombia. Patients with the absence of records in the medical charts of the variables of interest were excluded.

All subjects received the remission induction scheme proposed by the LN treatment guidelines of the American College of Rheumatology.[5]

As it was a pragmatic study, the decision to use cyclophosphamide or mycophenolate mofetil was left to the discretion

of the treating physician. These subjects had a standard clinical and paraclinical follow-up for 12 months (calculation of glomerular filtration rate, measurement of urinary sediment, and 24-h proteinuria).

Patients who did not achieve complete remission at 12 months were compared with those who accomplished this outcome. The definition of complete remission was adopted according to the AdHoc Subcommittee of the American College of Rheumatology on Lupus Nephritis criteria, as follows: glomerular filtration rate greater than or equal to 60 mL/min/1.73 m^2, a 15% rise from baseline in those patients with glomerular filtration rate less than 60 mL/min/1.73 m^2, proteinuria less than 0.5 g/24 h, inactive urinary sediment (less than five red blood cells, less than five leukocytes per high-power field and absence of hematic casts) and albumin serum greater than 3 g/L.[12]

Variables

The variables of interest were the use of medications in more than 80% of the follow-up time: antimalarials (chloroquine or hydroxychloroquine), angiotensin-converting enzyme (ACE) inhibitors (enalapril or captopril), angiotensin receptor blockers (ARB) (losartan), use of statins (lovastatin, simvastatin, atorvastatin), and the achievement of blood pressure levels below 130/80.

The data were obtained through the retrospective review of medical records, collected through a form previously established in a Microsoft Excel 2010 spreadsheet, with restriction of fields. All investigators received standard training before to the analysis of medical records and data collection.

Biases

The information on the variables of interest in the medical records was available in its entirety since the patient evaluation process is standardized in the places where the study was carried out. There were no losses to follow up. Since ACE inhibitors and ARB may have antiproteinuric and antihypertensive effects, their exact indication (antiproteinuric or antihypertensive) was taken into account from the data collection and analysis.

Sample size

The population is made up of all the patients with LN followed up for at least one year during the study period.

Statistical analysis

For the descriptive analysis of the quantitative variables, the measures of central tendency and dispersion were calculated, with their respective normality tests (Kolmogorov–Smirnov). The association between the variables of interest with the achievement of complete remission was determined using Pearson's Chi-square test. Association strengths odds ratio (OR) were calculated, with their respective confidence intervals (CI), with a level of 95%.

The Mann–Whitney *U* test was used to establish the relationship between the type of adjuvant therapy and the quantitative variables with non-normal distribution; Student's *t*-test was used for variables with a normal distribution. Once the factors associated with the achievement of partial or complete remission at 12 months had been established, the multivariate logistic regression model was proposed. The type of multivariate analysis used was "backward": all the variables were entered into the equation in the SPSS program and the variables that had the least partial correlation with the dependent variable were excluded. The goodness of the model was evaluated with the Hosmer and Lemeshow test.

Ethical considerations

The project was approved by the participating institutional ethics committees.

Results

General characteristics

167 potential patients were included. In all, their eligibility was confirmed through the inclusion and exclusion criteria; all subjects were analyzed. There were no missing data. The main characteristics of these patients are illustrated in Table 1.

Adjuvant therapies in lupus nephritis

142 subjects (85%) used antimalarials during the year of follow-up: 118 chloroquine and 24 hydroxychloroquine. Thus, 65.5% ($n = 73$) of the individuals used ACE inhibitors (enalapril) and 4.5% ($n = 5$) captopril, while 33.3% ($n = 56$) received ARB (losartan). In the entire cohort, 30.7% of the subjects had a dual-axis block. The indications for these drugs were: antiproteinuric effect (62% for ACE inhibitors and 38% for ARB); in the rest of the patients, the indication for these drugs was as

Table 1 – Baseline characteristics of a cohort of 167 Latin American mestizo patients with lupus nephritis in northwestern Colombia.

Characteristic	Value
Female gender (%)	83.9 ($n = 140$)
Age in years (mean and range)	24.7 (16–31)
Time elapsed between the diagnosis of SLE and LN (months) (median and interquartile range)	2 (0–35)
Proliferative lupus nephritis (class, % and *N*)	IV: 63.8 (107) III: 13.4 (22) V + III: 3.3 (6) V + IV: 3.3 (6)
Induction therapy with cyclophosphamide (%)	71.4
Induction therapy with mycophenolate mofetil (%)	25.9
Arterial hypertension (%)	28

141 patients with proliferative lupus nephritis were included.
Abbreviations: SLE: systemic lupus erythematosus; NL: lupus nephritis.

Table 2 – Factors associated with the absence of complete remission at 12 months in a cohort of patients with lupus nephritis (bivariate analysis).

Variable	OR	95% CI	*p* value
Use of chloroquine	0.58	0.24–1.39	0.262
Use of hydroxychloroquine	0.15	0.034–0.647	0.011
Achievement of blood pressure figures less than 130/80	0.25	0.1–0.615	0.003
Use of ACE inhibitors	0.59	0.308–1.163	0.17
Use of ARB	1.93	1.08–3.63	0.0053
Use of statins	2.81	1.42–5.54	0.003

Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers.

Table 3 – Factors associated with the absence of complete remission at 12 months in a cohort of patients with lupus nephritis (multivariate analysis).

Variable	OR	95% CI	*p* value
Use of chloroquine	0.589	0.237–1.467	0.256
Use of hydroxychloroquine	0.181	0.040–0.813	0.026
Achievement of blood pressure figures less than 130/80	0.271	0.107–0.684	0.006
Use of ACE inhibitors	0.717	0.355–1.446	0.352

Abbreviation: ACEIs: angiotensin converting enzyme inhibitors.

antihypertensive before the diagnosis of LN. Only 29.3% of the subjects ($n = 49$) used statins. Eighty-five percent of the individuals achieved blood pressure values below 130/80 at one year of follow-up.

Complete remission and association with adjuvant therapies

Complete remission at 12 months was only achieved in 39% of patients. In the bivariate analysis, the use of hydroxychloroquine and the achievement of blood pressure targets at 12 months were associated with the achievement of complete remission in this cohort, while the use of statins and ARB behaved as factors associated with failure in the achievement of remission (Table 2); in the multivariate analysis, the treatment with hydroxychloroquine and the achievement of blood pressure goals less than or equal to 130/80 were protective factors for failure to achieve remission at 12 months (Table 3). No significant association was found between the achievement of remission at 12 months of LN with the use of chloroquine, ACE inhibitors, ARB, statins, and with the dual blockade of the renin–angiotensin–aldosterone axis. The association between use of statins and non-achievement of renal remission found in the bivariate analysis did not stay in the adjusted model.

The model was adjusted ($p = 0.908$), but it explains only 13.3% of the variables that would be involved in the failure of therapy in these patients (Nagelkerke's $R^2 = 0.133$).

Discussion

The most important findings found in this study were that the use of hydroxychloroquine and the achievement of blood pressure levels below 130/80 were associated with remission in a cohort of Latin American mestizo patients with LN.

The renal protective effect of antimalarials in SLE patients has previously been demonstrated in several studies: Kasitanon et al. demonstrated that individuals with membranous nephritis treated with mycophenolate mofetil (MMF) were more likely to achieve remission after one year of treatment when they had also received hydroxychloroquine.[13] One of the strengths, in this regard, in our observational study, was that the protective effect of adjuvant therapies was independent of the cytotoxic drug used (cyclophosphamide or MMF). Supporting this beneficial effect, Barber et al. established that sustained renal remission (for at least three years after induction therapy) was more likely in subjects treated with hydroxychloroquine (93.8 vs 52.6%, $p = 0.010$).[14]

In the GLADEL cohort (Latin American Lupus Study Group), Pons-Estel et al. found that 64% of this cohort received hydroxychloroquine and a reduction in the rate of damage attributable to nephritis (OR 0.38, 95% CI: 0.25–0.58) was documented during a follow-up period of eight years.[15]

Dall Era et al.[16] found that the non-use of hydroxychloroquine was associated with treatment failure in the ALMS study (Aspreva Lupus Management Study); furthermore, Pons-Estel et al., in the North American multicenter LUMINA cohort (LUpus in MInorities, NAture versus nurture) found that this drug was able to delay the appearance of proliferative nephritis and proteinuria for up to 2.5 years.[17]

It is presumed that the pleiotropic effects of hydroxychloroquine: lipid-lowering, antiplatelet agents, inhibitors of Toll type 9 (TLR9) signaling, decreasing cytokine and prostaglandin production, inhibiting leukocyte activation, suppressing the presentation of autoantigens, decreasing the production of metalloproteases, in addition to their antiproliferative effects, would be responsible for a protective effect of the integrity and function in the glomeruli, avoiding the deposit of immune complexes, reducing oxidative stress and thus preventing organic damage.[18]

It was also striking that the use of hydroxychloroquine, but not chloroquine in the present study, both drugs being from the same group, was associated with remission in these subjects. It should be clarified that most of the studies have been done with hydroxychloroquine and there seems to be a specific effect, since, in the present work, for example, most of the subjects received chloroquine, but there was no greater remission with its use. Only one study by Sisó et al. was found, in which previous exposure to both chloroquine and hydroxychloroquine was associated with less development of kidney failure, thrombosis, infections, and arterial hypertension; unfortunately, this study does not accurately express how many individuals specifically received chloroquine or hydroxychloroquine.[19]

To date, it is not clear why hydroxychloroquine is more effective than chloroquine in NL; the biochemical and structural difference between both drugs would only account for fewer adverse effects; in 2010, a systematic review of antimalarials in SLE was carried out and most of the studies that support their beneficial effects in this entity were conducted with hydroxychloroquine.[20]

We also want to highlight the finding that the achievement of blood pressure values below 130/80, as recommended by the LN treatment guidelines[4] was associated with remission. The literature so far published in this regard, concludes the same message, but reporting the finding as a risk factor, not as a protector; that is, arterial hypertension is a predictor of chronic renal failure in this group of patients.[15,21,22] It should also be clarified that the design of these studies is different: the first was a prospective study; the second, similar to ours, was a nested case-control study; and the third is retrospective.

It has also been reported that arterial hypertension is associated with an earlier appearance of nephritis[23]; besides, its inadequate control during the first year of treatment is an adverse prognostic factor in this disease.[24] These arguments speak of the importance of this clinical factor in the remission of lupus nephritis and support the results obtained in the present study. In this sense, it should be clarified that, due to the small number of individuals who received ACE or ARB, it is not possible to attribute blood pressure control to the use of these drugs; control of glomerulonephritis with immunosuppression could be responsible, for the most part, for this outcome.

We also want to highlight the scarce publication that exists on the use of statins, ACE inhibitors, and ARB in LN; they appear in management guidelines[5] but are extrapolated from non-lupus nephropathies. To our knowledge, there is only one study of fluvastatin in murine models of LN in graft-versus-host disease, where reduction of the expression of the mitogen-activated protein kinase p38 (p38MAPK) was demonstrated.[25] In this study the use of statins was associated with non-achievement of remission of lupus nephritis in the bivariate analysis; however, this association did not stay in the multivariate model. The indication to use statins was hyperlipidemia maybe associated with nephrotic syndrome; thus, the association between statins and non-achievement of renal remission could be spurious. This topic must be explored in future studies.

Regarding the antiproteinuric effect of blocking the renin–angiotensin–aldosterone axis, one of the first evidence was in silent nephritis, different from the proliferative nephritis analyzed in our study.[26] In 1990, a case of a 22-year-old patient with membranous lupus nephritis refractory to immunosuppressants with a reduction of proteinuria by more than 50% at 16 weeks with 125 mg of captopril was reported.[27]

There is also a retrospective report of seven patients with SLE who received enalapril 5 mg and losartan 50 mg for uncontrolled proteinuria; at 12 months, there was a reduction of this up to 84%, in addition to a reduction in blood pressure levels.[28]

Durán-Barragán et al. found that the use of ACE inhibitors in the LUMINA cohort increased the probability of survival free of nephritis and disease activity; it should be noted that only 21% of these patients received ACE inhibitors. This study also does not clearly define the ACE inhibitor used, the dose, and the time of use before the development of nephritis, fundamental variables to establish any causal association.[29] In murine models of LN, there is also evidence of antiproteinuric efficacy and stabilization of renal function of aldosterone blockade with spironolactone, reducing the inflammatory response and apoptosis in the process of glomerulonephritis.[30]

Furthermore, it is interesting to mention that the effect of these drugs is not only antihypertensive but probably immunomodulatory. Daza et al. evaluated 18 patients with LN, evaluating the nitrogen level and proteinuria; they showed that the combination of captopril and cyclophosphamide improved both outcomes at six months; this impact was independent of glomerular filtration rate or renal plasma flow; it is attributed to the reduction of urinary levels of PGE2.[31] In murine models of LN, a delay in the appearance of proteinuria has been demonstrated through the inhibition of TGF-beta, IL-4, and IL-10.[32]

Several limitations of this study are recognized, most of them attributable to its retrospective design; the absence of long-term follow-up that demonstrates the persistence and consistency of the results found; the infrequent use of statins and dual blockade of the renin–angiotensin–aldosterone axis, which could explain the fact that no type of association was found with the clinical outcomes of interest, and even that OR behaved as a factor risk for failure to achieve remission in the bivariate analysis, a fact that has no biological plausibility and is explained by the phenomenon of reverse causality; this spurious association disappeared in the adjusted analysis.

It is also recognized that the multicenter and multiethnic nature of cohorts such as GLADEL and LUMINA gives these studies greater precision and generalizability of the results.

It is believed, however, that the results of this study can be generalized to Latin American mestizo patients with LN, since individuals from everyday clinical practice diagnosed with the gold standard (renal biopsy) were included, following the current classification (ISN/RPS 2003), and who were treated with conventional immunosuppressive regimens.

Conclusion

In a cohort of patients with lupus nephritis, the use of hydroxychloroquine and achieving blood pressure values lower than 130/80 were associated with remission at 12 months.

Declaration of conflicts of interest and funding sources

The authors declare that they have no conflicts of interest nor did they receive money from any institution. The participating institutions offered the research group all the logistical support necessary to carry out the data collection and preparation of the research article.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2021.03.010.

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