Reumatología Clínica

Original Article

Predictive Risk Factors for Failure to Induction Therapy of Lupus Nephritis in a Cohort of Colombian Patients☆

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A B S T R A C T

Objectives: To determine the predictors of failure to obtain remission after induction therapy for proliferative lupus nephritis in a group of northwestern Colombian patients.
Material and methods: A retrospective study was conducted. We included patients with systemic lupus erythematosus according to the American College of Rheumatology criteria who had nephritis confirmed by renal biopsy.
Results: We followed 84 patients: 88.1% female, and 11.9% male. The mean age at diagnosis of systemic lupus erythematosus was 27.5±11.8 years (9–70). The average time between diagnosis of systemic lupus erythematosus and proliferative nephritis onset was 13.6 months (0–168). Histopathologic type: IV (78.57%), III (15.47%), III–IV/V (5.96%). Activity index: 6.7±4.6. Chronicity index: 2±2.7. 24-hour proteinuria (mg): 6164 (130–18,100). Baseline creatinine: 1.14 mg/dL (0.43–7.4). Induction therapy: Steroids (100%), cyclophosphamide (76.2%) and mycophenolate mofetil (23.8%). At six months, 56% of individuals failed to achieve partial or complete remission. Predictors of failure to induction therapy were, in accordance with the bivariate analysis (OR; 95% CI): creatinine level more than 1.2 mg/dL (10.8; 3.18–36.84; *P*<.005), nephrotic range proteinuria (11.9; 3.09–45.8; *P*<.001), and an activity index above 8 (5.04; 1.7–14.3; *P*<.001). In the multivariate analysis, only baseline creatinine higher than 1.2 mg/dL (10.92; 2.65–45.02; *P*=.001), and nephrotic range proteinuria (9.81; 1.85–52.04; *P*=.007) were significant.
Conclusions: A significant percentage of Colombian patients fail to achieve remission of proliferative lupus nephritis after six months of treatment.

Factores de riesgo predictores de falla a la terapia de inducción de nefritis lúpica en una cohorte de pacientes colombianos

R E S U M E N

Objetivos: Determinar los predictores de falla a la inducción de remisión de la nefritis lúpica proliferativa en pacientes del noroccidente colombiano.
Material y métodos: Estudio pragmático con análisis retrospectivo. Se incluyeron sujetos con lupus eritematoso sistémico por criterios del *American College of Rheumatology* con nefritis confirmada por biopsia renal.
Resultados: Se analizaron 84 pacientes (88,1% mujeres y 11,9% hombres). Edad al diagnóstico del lupus eritematoso sistémico: 27,5±11,8 años (9–70). Tiempo entre el diagnóstico de lupus eritematoso y nefritis proliferativa: 13,6 meses (0–168). Clase histológica: IV (78,57%), III (15,47%), III–IV/V (5,96%). Índice de actividad: 6,7±4,6. Índice de cronicidad: 2±2,7. Proteinuria (mg/24 h): 6.164 (130–18.100). Creatinina basal: 1,14 mg/dl (0,43–7,4). Terapia de inducción: esteroides (100%), ciclofosfamida (76,2%) y micofenolato mofetil (23,8%). A los 6 meses fallaron en lograr remisión parcial o completa el 56% de los individuos. Los predictores de falla a la terapia de inducción fueron, en el análisis bivariado (OR; IC 95%):

creatinina mayor 1,2 mg/dl (10,8; 3,18–36,84; p < 0,005), proteinuria en rango nefrótico (11,9; 3,09–45,8; p < 0,001) e índice de actividad mayor de 8 (5,04; 1,7–14,3; p < 0,001). En el análisis multivariado solo fueron significativos creatinina basal mayor de 1,2 mg/dl (OR: 10,92; IC 95%: 2,65–45,02; p = 0,001) y la proteinuria en rango nefrótico (OR: 9,81; IC 95%: 1,85–52,04; p = 0,007).

Conclusiones: Un porcentaje significativo de pacientes colombianos con nefritis lúpica proliferativa fallan en lograr remisión a los 6 meses.

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with variable clinical features. The frequency of organ involvement and severity vary depending on ethnicity, gender and age of onset.[1–5]

Lupus nephritis (LN) occurs in 30% of caucasian patients and 60% of African Americans[3]; in our geographical area, between 50 and 55% of adults.[6] 7% and 75 children with SLE[8] present LN sometime during their disease progression.

In the GLADEL cohort[1] (Latin American Lupus Study Group), 51.7% of patients had LN. In this cohort, 58.3% of mestizos lupus patients, 58.3% of African-American and 43.6% of caucasians suffered LN at some point in their evolution.

Between 10 and 25% of SLE patients progress to chronic renal failure (CRF).[9,10] Proliferative forms of LN (types III, IV and V associated forms of III or IV) are the most common and serious and can lead to ESRD.[11]

Baseline levels of creatinine and proteinuria, the presence of hypertension (HT), anti-DNA antibodies, low levels of C3 and C4, high levels of activity and chronicity and Hispanic and African American ethnicity have been identified as poor long-term prognosis factors in patients with proliferative LN.[12–21]

The current treatment of LN includes an induction of remission phase with high-dose steroids associated with pulse cyclophosphamide (CFM) or mycophenolate mofetil (MMF) and a maintenance phase with low doses of steroids associated with quarterly CFM, MMF or azathioprine (AZA).[11]

The failure to achieve partial or complete remission at 6 months is associated with poor long-term prognosis and involves greater use of immunosuppressive drugs.[11]

Few studies have evaluated the impact of early renal response of LN and in the long-term prognosis, baseline creatinine, proteinuria in the nephrotic range, high rates of chronicity and activity, hypocomplementemia and high titers of anti-DNA are poor prognostic factors,[10–17] while the normalization of creatinine in the first 48[22] weeks and decreased proteinuria in the first 52 weeks are good prognostic markers.[23]

Normalization of creatinine and proteinuria decreasing to less than 1 g in 24 h were independent predictors of good long-term prognosis in the[24] *Eurolupus Nephritis Trial.*

In Asian patients a longer time to achieve remission and a lack of complete remission are independent predictors of renal relapse, and higher baseline creatinine and failure to achieve complete remission in the first 6 months were independent predictors IRC.[25]

To our knowledge, no studies have evaluated the predictive factors of failure in inducing remission in LN in a predominantly Hispanic population of Latin American mestizos; in addition, studies that have so far evaluated prognostic factors have ESRD as the primary outcome, not response to induction therapy in the first 6 months, hence, the identification of predictors of early therapeutic failure could help select treatments more appropriately in this population with a poor prognosis.

The objective of this study is to define the factors that predict failure of induction therapy in proliferative LN in a cohort of Latin American mestizo patients.

Materials and Methods

We performed a retrospective consecutive review of a prospective cohort of all patients with 4 or more classification criteria of the *American College of Rheumatology* (ACR) for SLE, followed at the Pablo Tobon Uribe Hospital, Medellín (Colombia) between January 2004 and December 2010.

The study population consisted of patients diagnosed with proliferative LN[26] (histology classes III, IV and V in which glomerulonephritis type III or IV) as classified by the *International Society of Nephrology/Renal Pathology Society* (ISN/RPS) 2003 coexist; patients received remission induction therapy with CFM 500–1000 mg/m^2 body surface monthly or MMF 2 g via daily orally for 6 months. Children received doses of cyclophosphamide 500 mg/m^2 of body surface and mycophenolate mofetil 20–40 mg/kg/day. All patients received prednisolone 1 mg/kg/day for 4 weeks and then underwent gradual dose reduction down to 10 mg/day within 4 weeks.

Being a pragmatic clinical practice study, the decision to use CFM or MMF as induction therapy was made by the treating physician.

Primary Outcomes

These were determined at the end of induction therapy based on response criteria for proliferative and membranous renal disease in clinical studies of SLE established by the Ad Hoc Subcommittee of the ACR for[27] lupus nephritis.

Complete remission. Defined as glomerular filtration rate (GFR) greater than 90 ml/min/1.73 m^2 of body surface area, less than 500 mg/24 h proteinuria, inactive urinary sediment (no cell casts and leukocyte and less than 5 erythrocytes and leukocytes per high-power field).[27]

Partial remission. 25% improvement in GFR, improvement of at least 50% of 24-h proteinuria inactive urinary sediment.[27]

Baseline impaired renal function. Serum Creatinine at the beginning of induction therapy of 1.2 mg/dl or greater.[24]

Nephrotic range proteinuria. 24 h proteinuria greater than or equal to 3500 mg/m^2 body surface.[27]

Candidates variables to be risk factors for failure of remission induction were chosen based on the literature. We included: age at diagnosis, sex, creatinine, proteinuria 24 h, serum albumin, presence of hypertension, C3 and C4 hypocomplementemia, anti-DNA antibodies, IgG and IgM anticardiolipin antibodies, histological classes LN, activity indices and chronicity of the same classification and the use of CFM or MMF as induction therapy.[10–26]

Statistical Analysis

For the descriptive analysis of quantitative variables we employed measures of central tendency and dispersion, with their respective normality tests.

For each case (failure to achieve complete or partial remission at 6 months) a control from the same cohort (achieving partial or complete remission at 6 months) was assigned. To analyze the association between patient age and the age at diagnosis of SLE, with the failure of induction of remission therapy we used the Student's *t*-test (mean difference) which had normal distribution, and the