# Avaliação de 100 pacientes com nefrite lúpica acompanhados por dois anos

## *Analysis of 100 patients with lupus nephritis followed up for 2 years*

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## RESUMO

**Objetivos**: Determinar a frequência de remissão total e parcial no tratamento da nefrite lúpica aos 12 e 24 meses de seguimento. Comparar esses subgrupos aos 12 meses, correlacionando as variáveis renais iniciais com a resposta ao tratamento. Analisar e comparar os resultados terapêuticos do subgrupo com glomerulonefrite proliferativa difusa por correlação clínico-patológica ("classe IV clínica") com aqueles de "classe IV histológica", isto é, com biópsia renal comprovada pela Organização Mundial da Saúde. **Material e métodos**: Foram estudados 100 pacientes consecutivos com diagnóstico de lúpus eritematoso sistêmico (LES) e nefrite, atendidos no Serviço de Reumatologia da Santa Casa de Misericórdia de São Paulo e acompanhados por dois anos. Os portadores de comorbidades que comprometem os rins foram excluídos. Foram analisadas as variáveis demográficas, clínicas, laboratoriais e o índice de atividade da doença (SLEDAI). Os pacientes com classe histológica III, IV ou V receberam corticosteroide e ciclofosfamida como tratamento de indução da nefrite lúpica e aqueles com classe II receberam apenas corticosteroide. **Resultados**: A idade média ao diagnóstico de LES foi de 24,71 ± 10,14 anos, com predomínio do sexo feminino (88%). O SLEDAI calculado ao diagnóstico foi de 16,09 ± 6,48. Em relação às variáveis renais iniciais, a creatinina média foi de 1,02 ± 0,49 mg/dL, a proteinúria de 24 horas média foi de 2,57 ± 2,39 g e o anticorpo anti-dsDNA foi encontrado em 66% dos casos. Todos os pacientes receberam corticosteroide e 75% utilizaram a ciclofosfamida. Cinquenta e seis pacientes foram submetidos à biópsia renal. Os subtipos II e IV foram os mais prevalentes (33,9% e 32,2%, respec-

## *ABSTRACT*

***Objectives:*** *To assess the frequency of total and partial remission in the treatment of lupus nephritis at 12 months and 24 months. To compare these subgroups at 12 months and correlate the initial renal variables with the therapeutic response. To analyze and to compare the therapeutic results of the subgroup with diffuse proliferative glomerulonephritis by clinicopathological correlation ("clinical class IV") with those with biopsy-proven WHO class IV ("histological class IV").* ***Patients and methods:*** *One hundred consecutive patients with diagnosis of systemic lupus erythematosus (SLE) and nephritis who attended to the department of rheumatology of a tertiary referral center were studied. The length of the follow up was 2 years. Patients with comorbidities that compromise the kidneys had been excluded. The demographic, clinical and laboratory variables and the disease activity index (SLEDAI) were analyzed. Patients with lupus nephritis WHO class III, IV or V received glucocorticoid and cyclophosphamide for induction of remission and those with class II received only glucocorticoid.* ***Results:*** *The average age at SLE diagnosis was of 24.71 + 10.14 years, with a predominance of female gender (88%). The initial SLEDAI was 16.09 ± 6.48. At the time of the diagnosis of nephritis, mean serum creatinine was 1.02 ± 0.49 mg/dL, mean 24-hour urinary protein level was of 2.57 ± 2.39g and the antibody anti-dsDNA was found in 66% of the cases. All the patients had received glucocorticoids and 75% had used cyclophosphamide. Fifty-six patients had been submitted to renal biopsy. The most prevalent subtypes were class II and IV (33.9% and 32.2%, respectively).*

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tivamente). Após 12 meses de acompanhamento, todos os pacientes apresentaram redução significativa da proteinúria de 24 horas, melhora do sedimento urinário e dos valores das frações do complemento (C3, C4, CH50). A frequência de remissão total aos 12 meses foi 72,7% e, aos 24 meses, 85,7% ($p = 0,013$). A remissão parcial ocorreu em 27,3% dos doentes aos 12 meses e em 14,3% aos 24 meses. O sexo masculino apresentou menor frequência de remissão total comparado ao feminino aos 12 meses de acompanhamento (45,5% *versus* 81,6%, $p = 0,007$). Dentre as diferentes variáveis estudadas, nenhuma se correlacionou com remissão total ou parcial aos 12 meses. O subgrupo "classe IV clínica" apresentou maior frequência de remissão total que o subgrupo "classe IV histológica". **Conclusão**: Com o esquema terapêutico usado em nosso serviço, verificou-se um excelente desfecho em dois anos. Não foram observadas correlações entre variáveis clínico-laboratoriais e remissão total ou parcial. O sexo masculino apresentou menores taxas de remissão total comparado ao feminino. Apesar do pequeno número de pacientes estudados e das controvérsias quanto à biópsia renal, a taxa de remissão total foi maior nos pacientes com "classe IV clínica" em relação àqueles com "classe IV histológica".

**Palavras-chave**: lúpus eritematoso sistêmico, nefrite, remissão total, biópsia renal.

*After 12 months, all the patients had significant reduction in the 24-hour urinary protein level, improvement in the urinary sediment and increase in the fractional values of the complement (C3, C4, CH50). The frequency of total remission at 12 months was 72.7% and, at 24 months, 85.7% (p =0.013). Partial remission occurred in 27.3% at 12 months and, in 14.3%, at 24 months. Male gender presented a lower rate of total remission compared with women at 12 months (45.5% versus 81.6%, p = 0.007). Among several factors studied, none was correlated with total or partial remission at 12 months. The subgroup "clinical class IV" presented a higher frequency of total remission than the subgroup "histological class IV".* ***Conclusion:*** *Our therapeutic approach achieved an excellent outcome in two years. Correlations between clinical and laboratory variables and total or partial remission were not observed. Male gender presented a lower rate of total remission compared with women. Despite the small number of patients studied and the controversies of renal biopsy, the rate of total remission was higher in patients with "clinical class IV" than in those with "histological class IV".*

***Keywords:*** *systemic lupus erythematosus, nephritis, complete remission, renal biopsy.*

## INTRODUÇÃO

O lúpus eritematoso sistêmico (LES) é uma doença inflamatória crônica, de natureza autoimune, que pode afetar múltiplos sistemas orgânicos. O envolvimento renal no LES é uma causa significativa de morbidade e mortalidade devido à possibilidade de progressão para insuficiência renal e a complicações relacionadas ao tratamento. Pelos critérios do Colégio Americano de Reumatologia (American College of Rheumatology, ACR – 1997), a nefrite lúpica é definida pela presença de proteinúria persistente (> 0,5g nas 24 horas) ou maior que 3+ ou pela cilindrúria (cilindros hemáticos, tubulares, granulosos ou mistos). Entre os padrões histológicos elaborados pela Organização Mundial da Saúde (OMS), a glomerulonefrite proliferativa difusa (classe IV) representa o subtipo mais prevalente e o de pior prognóstico.[1] A nefrite constitui a principal causa de internações e mortalidade entre os pacientes com LES.[2]

Estudos randomizados anteriores demonstraram que o uso da ciclofosfamida para o tratamento da nefrite lúpica se correlaciona com maiores taxas de preservação da função renal a longo prazo e com menor incidência de doença renal terminal.[3]

Existem controvérsias quanto à indicação de biópsia renal em todos os pacientes com LES e nefrite. Esdaile *et al*. estabeleceram uma correlação entre os achados clínico-laboratoriais e a classificação histológica da nefrite lúpica, com o intuito de orientar a conduta terapêutica e racionalizar a realização de procedimentos invasivos nessa população[4] (Tabela 1).

Este trabalho foi desenvolvido para demonstrar a experiência de um serviço terciário no tratamento da indução e manutenção da remissão da nefrite lúpica. Sabe-se que esse é um dos temas de maior relevância na Reumatologia, apesar do pequeno número de publicações sobre o assunto em nosso meio, somado às controvérsias quanto à indicação de biópsia renal nesses pacientes. Os objetivos principais deste estudo são determinar a frequência de remissão total e parcial da nefrite aos 12 e 24 meses de acompanhamento; comparar esses subgrupos aos 12 meses, correlacionando as variáveis renais iniciais com a resposta terapêutica e demonstrando a experiência de um serviço brasileiro no manejo das manifestações renais do LES. Outro objetivo é comparar os resultados terapêuticos dos subgrupos de pacientes com glomerulonefrite proliferativa difusa por correlação clínico-patológica ("classe IV clínica") daqueles com "classe IV histológica", ou seja, com biópsia renal.

## MATERIAL E MÉTODOS

Trata-se de uma análise retrospectiva de prontuários de pacientes com diagnóstico de LES e nefrite, segundo os critérios de classificação do ACR de 1997, atendidos no Serviço de Reumatologia da Santa Casa de Misericórdia de São Paulo, no período de 1990 a 2003. A nefrite lúpica é definida pela presença de proteinúria persistente (> 0,5g nas 24 horas) ou maior que 3+ no EAS ou pela cilindrúria (cilindros hemáticos, tubulares, granulosos ou mistos).

com hipertensão arterial no início da doença, com o anti-DNA positivo e com o uso de ciclofosfamida. Possíveis explicações para esses fatos discrepantes decorrem, principalmente, de diferenças metodológicas das séries: critérios de inclusão e seleção de pacientes, estudos retrospectivos, tempos de acompanhamento, tratamentos realizados, definição dos desfechos clínicos, tamanho da amostra, entre outros.

O sexo masculino apresentou menores taxas de remissão total aos 12 meses comparado ao feminino, o que poderia sugerir pior prognóstico da nefrite lúpica entre os homens na nossa casuística. Esse dado difere da literatura em que se demonstra que o sexo do indivíduo não apresenta valor prognóstico na evolução da nefrite lúpica.[16]

Apesar do pequeno número de pacientes estudados e das controvérsias quanto à biópsia renal inicial, as taxas de remissão nos pacientes com "classe IV clínica" e "classe IV histológica" foram altas aos 12 meses. Um balanço entre os ganhos potenciais de informações que podem guiar um esquema terapêutico e as complicações inerentes ao procedimento invasivo sempre deve ser levado em consideração antes de indicar a biópsia renal. Estudos prévios demonstraram que parâmetros clínico-laboratoriais são capazes de predizer com acurácia o prognóstico da nefrite lúpica, sem a necessidade de biópsia em todos os casos com envolvimento renal.[17,18] Já outros estudos advogam que os dados histológicos oferecem informações adicionais aos parâmetros laboratoriais e podem guiar, de maneira mais precisa, a escolha terapêutica.[19] Como pode ser percebido, o tema permanece controverso. Na experiência do nosso serviço, a biópsia renal é individualizada e indicada, sobretudo, nas seguintes situações: dúvida quanto à correlação clínico-histológica, presença de síndrome nefrótica, ou em casos que não responderam à terapia de indução com ciclofosfamida. Pelo presente estudo, a frequência de remissão total aos 12 meses foi significativamente mais alta nos pacientes com "classe IV clínica", sem a necessidade de informações adicionais pelo exame histológico. Na casuística apresentada, as variáveis renais e do LES, bem como a dose cumulativa da ciclofosfamida não diferiram entre os pacientes com "classe IV histológica" ou "clínica", isto é, com e sem biópsia renal.

Portanto, concluímos que, neste estudo, a realização de biópsia renal para a determinação do subtipo histológico não influenciou na resposta ao tratamento em pacientes com nefrite lúpica acompanhados por dois anos. Os dados apresentados demonstraram que a correlação clínico-histológica pode ajudar na decisão terapêutica desses pacientes, reservando a biópsia renal apenas para situações especiais.

# *Analysis of 100 patients with lupus nephritis followed up for 2 years*

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune chronic inflammatory disease that may affect multiple systems. Renal involvement in SLE is a significant cause of morbidity and mortality due to the possibility of progression to end stage renal disease (ESRD) and treatment-related complications. By the criteria of the American College of Rheumatology (ACR – 1997), lupus nephritis is defined by the presence of persistent proteinuria (> 0,5g in 24 hours), or higher than 3+, or by cylindruria (hematic, tubular, granular or mix cylinder). Among histological standards created by World Health Organization (WHO), diffuse proliferative glomerulonephritis (class IV) represents the most prevalent and worst prognostic subtype.[1] Nephritis is the main cause of hospitalization and mortality among SLE patients.[2]

Controlled trials have shown that the use of cyclophosphamide for lupus nephritis treatment is correlated with higher rates of long term renal function preservation and lower incidence of ESRD.[3]

There are controversies about indicating renal biopsy to every lupus patients with nephritis. Esdaile *et al*. established a correlation between clinical and laboratory findings and histological classification of lupus nephritis, in order to guide therapeutic approach and rationalize the performance of invasive procedures in such population.[4] (Table 1)

This study was designed to demonstrate a tertiary hospital experience in the treatment of induction and maintenance of remission of lupus nephritis. This is one of the most relevant topics in Rheumatology, although there are few publications on it, added to the controversy about the indication of renal biopsy in these patients. The main objectives of this study are to establish the frequency of complete and partial remission of nephritis both at 12 and 24 months; to compare these subgroups at 12 months, with correlation between initial renal variables with therapeutic response; and to demonstrate the experience of a Brazilian centre in treating SLE renal manifestations. Another endpoint is to compare the therapeutic results of the subgroup with diffuse proliferative glomerulonephritis by clinicopathological correlation ("clinical class IV") with those with biopsy-proven WHO class IV ("histological class IV").

**Table 1**
Correlation between clinical and laboratory findings and histological classification of lupus nephritis

| | Class II | Class III | Class IV | Class V |
|---|---|---|---|---|
| Arterial hypertension | None | Rare | Frequent | Rare |
| Proteinuria (grams/24hours) | < 1 | < 2 | 1-20 | 3,5-20 |
| Hematuria Erythrocytes/per field) | 5-15 | 5-15 | > 15 | None |
| Leucocyturia/leucocytes per field) | 5-15 | 5-15 | > 15 | None |
| Creatinine (mg/dl) | Normal | Normal or incremented | Frequently incremented | Normal |
| Glomerular filtration rate (ml/min) | Normal | 60 - 80 | < 60 | Normal |
| CH50 | ↓ | ↓ | ↓↓ | Normal |
| C3 | ↓ | ↓ | ↓↓ | Normal |
| Anti-dsdna | ↑ | ↑ | ↑↑ | Normal |

Esdaile, 1991 and 1992

## MATERIAL AND METHODS

Retrospective chart analysis was done for patients with SLE and nephritis who attended the Rheumatology Department at Santa Casa de Misericórdia de São Paulo from 1990 to 2003. Lupus nephritis is defined according the ACR criteria as persistent proteinuria (> 0,5 g in 24 hours) or higher than 3+ or by cylindruria (hematic, tubular, granular or mix cylinders).

Patients who had been submitted to initial renal biopsy or not have been included. Classification of nephritis had been clinically established according to Esdaile[4] or by histopathology. Renal biopsy was individually assigned based, mainly, on the following situations: difficulty to establish a clinicopathological correlation (doubtful cases), presence of nephrotic syndrome and/or to support therapeutic decision.

Patients had been followed up for two years since nephritis was diagnosed and therapy started, based on clinicopathological correlation or on renal biopsy data. Our therapeutic approach included high doses of corticosteroids (prednisone 1-2 mg/kg/day orally) in every patient or 1g/day doses of methylprednisolone intravenously, during 3-5 consecutive days, in more severe cases. Intravenous (IV) monthly cyclophosphamide was used in 0.5 to 1 g/m$^2$ doses of body surface area as a first-choice of immunosuppressive agent for induction of class III, IV or V nephritis remission. Azathioprine or mycophenolate mofetil (MMF) were used for nephritis maintenance treatment after 6-9 months of cyclophosphamide IV, or in case of failure or intolerance to the approach described before. Patients with mesangial glomerulonephritis were treated only with high doses of glucocorticoid.

Therapeutic response was evaluated after 12 and 24 months. Boumpas & Balow (1998) criteria were used to classify therapeutic response as complete, partial and no response.[5] According to these authors, complete remission is defined as stabilization or normalization of serum creatinine, urinary sediment with less than five erythrocytes per field and 24-hour proteinuria lower than 1.0 g for, at least, six months. Partial remission is characterized by stabilization or improvement of serum creatinine, hematuria lower than five cells per field and persistent 24-hour proteinuria reduction (if nephrotic, reduction higher than or equal to 50%, but with value lower than 3,0 g/24 hours; if non nephrotic, reduction higher than or equal to 50%, but with value higher than 1.0 g/24 hours). When presenting with renal function deterioration (excluding other causes, like sepsis, nephrotoxic drugs, renal vein thrombosis), proteinuria increment or reduction not meeting criteria above, patients were considered as no response.

Patients with comorbidities that compromise the kidneys were excluded from this study. The demographic, clinical and laboratory variables and the *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI) were analyzed. In order to verify the influence of different factors in nephritis prognosis, patients were divided into groups of complete and partial remission, "clinical class IV" and "histological class IV".

Data were expressed as mean ± standard deviation. The program used for statistical analysis was SPSS version 13.0. Comparison between means was performed using "*t*" Student test, and comparison between frequencies was done with McNemar and chi-square tests. When $p < 0,05$, difference was considered significant.

This study had been previously approved by the Research Ethics Committee of the institution.

## RESULTS

Records of 100 patients with lupus nephritis were analyzed during two years. The average age at SLE diagnosis was 24.71 ± 10.14 years, ranging from 5 to 46 years old. The average age at lupus nephritis diagnosis was 26.78 ± 10.95 years, ranging from 5 to 53 years. Period of time between SLE and nephritis diagnosis was 2.32 ± 4.70 years. In this trial, 88% were female and predominantly caucasian (Table 2).

The main extra-renal SLE manifestations were joints, mucous-cutaneous, hematologic and serositis, found in 81%, 79%, 67% and 24% of the patients. Neuropsychiatric lupus occurred in 11% of patients. The average SLEDAI value at diagnosis was 16.09 ± 6.48, expressing disease in considerable activity, that is, SLEDAI ≥ 4.

Baseline average serum creatinine was 1.02 ± 0.49 mg/dL, ranging from 0.4 to 3.6 mg/dL, and average proteinuria was 2.57 +2.39 grams/24 hours. At the time of nephritis diagnosis, 33% of patients were hypertensive according to criteria proposed by World Health Organization[6] and 66% had high titers of antibody anti-dsDNA (Table 3).

Fifty-six patients had been submitted to percutaneous renal biopsy. The most frequent histological subtypes were WHO class II and IV (33.9% and 32.2%, respectively). Glomerulonephritis class III was observed in 11 of 56 patients (19.6%) and only eight patients presented class V (14.3%). Out of 44 patients who had not been submitted to renal biopsy, 6 had clinical and laboratory data compatible to mesangial glomerulonephritis, 11 with focal proliferative glomerulonephritis, 23 with diffuse proliferative and 4 with membranous.

Regarding the treatment, all patients received glucocorticoid for nephritis, and prednisone had been used in 100% of the cases. Out of 100 patients, 75% used IV cyclophosphamide, since they presented glomerulonephritis class III, IV or V, due to clinical- histological correlation or renal biopsy; with cumulative doses of 9.44 ± 4.22 grams. Fifteen patients received IV cyclophosphamide and methylprednisolone. Among patients using cyclophosphamide, 60 (80%) completed remission induction period and, then, received 2-3 mg/kg/day doses of azathioprine for maintenance treatment. Fifteen patients discontinued cyclophosphamide due to intolerance or adverse effects, such as gastrointestinal effects (nausea and vomit in 8 patients), infections (5 patients) and severe leucopenia (< 2000 cells/mm³ in 4 individuals). In case of cyclophosphamide discontinuation during induction phase, azathioprine was administered in 10 patients, and mycophenolate mofetil was used in 5 cases, in a 2 g/day doses, taken twice a day. Most patients with cutaneous and articular manifestations (85%) were taking antimalarials (6 mg/kg/day of hydroxychloroquine or 4 mg/kg/day of chloroquine diphosphate).

Renal variables analyzed were: Serum creatinine, 24-hour proteinuria, changes in urinary sediment and fractional complement. Comparing such variable results at the beginning and after 12 months of follow-up, it was found that all patients showed significant reduction in the 24-hour urinary protein level, improvement in the urinary sediment and increase in the fractional values of the complement (Table 4). During follow-up, there was a trend to increment serum creatinine, without, however, reaching statistic significance.

Complete remission frequency at 12 month was 72.7%, and at 24 months, 85.7% ($p$ = 0,013). Partial remission was achieved in 27.3% of patients at 12 months, and 14.3% at 24 months (Figure 1). Comparison among subgroups with complete and partial remission at 12 months and the baseline parameters of SLE and nephritis showed that no variable had correlation with therapeutic response (Table 5). Renal flare during nephritis treatment was observed in 40% of cases, most of them (80%) during maintenance phase. In such cases, glucorticoid and immunosuppressive doses were optimized, according to doses intervals described above.

Male patients presented a lower rate of complete remission when compared with female at 12 months (45.5% versus 81.6%, respectively, $p$ = 0.007), which could suggest a less favorable outcome of lupus nephritis among men of this population. (Figure 2). As may be verified by the presented data, men who did not achieve complete remission at 12 months did accomplish partial response to the established treatment.

Comparative analysis of "clinical class IV","histological class IV", and initial variables of nephritis and SLE, showed that there was no statistical difference among SLEDAI values, serum creatinine and 24-hour proteinuria, as well as in the urinary sediment, the fraction values of complement and the cumulative doses of cyclophosphamide in both groups (Table 6). The rate of complete remission was higher in patients with "clinical class IV" than in those with "histological class IV". (Figure 3)

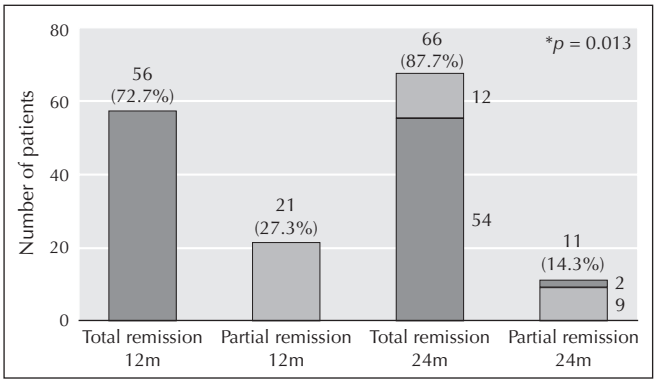
## DISCUSSION

In this study, we report the evolution of 100 patients with lupus nephritis followed up for two years. The treatment regimen of our centre used IV cyclophosphamide as a first-choice immunosuppressive agent for induction of class III, IV or V nephritis remission. Other agents like azathioprine or MMF were used for nephritis remission-maintenance treatment after 6-9 months IV cyclophosphamide, or in case of failure or intolerance to the previously described regimen. According to Contreras *et*

**Table 2**
Analysis of 100 patients with lupus nephritis followed up for 2 years. Demographic data.

| | |
|---|---|
| Age at SLE diagnosis in years (M ± SD) | 24.71 ± 10.14 (5-46) |
| Age at nephritis diagnosis in years (M ± SD) | 26.78 ± 10.95 (5-53) |
| Interval between SLE diagnosis and nephritis diagnosis in years (M ± SD) | 2.32 ± 4.70 (0-24) |
| Women (%) | 88 (88%) |
| Race (%) | |
| White | 57 (57%) |
| Others | 29 (29%) |
| Non registered | 14 (14%) |

SLE = Systemic Lupus Erythematosus; M = mean; SD = standard deviation.




*Mc Nemar test

**Figure 1.** Comparison among subgroups with total and partial remission at 12 months and 24 months of follow-up (n = 77).

**Table 3**
Initial clinical and laboratory data of 100 patients with lupus nephritis

| | |
|---|---|
| Creatinine in mg/dL (M ± SD/variation) | 1.02 ± 0.49 (0.4-3.6) |
| Proteinuria in g/24h (M ± SD/variation) | 2.57 ± 2.39 (0-10.3) |
| SAH (%) | 37 (37%) |
| Anti-dsDNA positivity (%) | 66 (66%) |

M = mean; SD = standard deviation; SAH = Systemic Arterial Hypertension; Anti-dsDNA = double-stranded-dsDNA.

**Table 4**
Comparison of variables related to nephritis at baseline ($T_0$) and after 12 months ($T_{12}$) in 100 patients with lupus nephritis

| | $T_0$ | $T_{12}$ | *P** |
|---|---|---|---|
| Creatinine in mg/dL (M ± SD) | 0.99 ± 0.42 | 1.03 ± 0.94 | 0.663 |
| Proteinuria in g/24h (M ± SD) | 2.58 ± 2.42 | 1.26 ± 1.83 | 0.000 |
| Hematuria in cell p/f (M ± SD) | 22.99 ± 23.42 | 13.06 ± 18.64 | 0.000 |
| Leucocituria in cell p/f (M ± SD) | 14.61 ± 16.77 | 10.10 ± 15.34 | 0.037 |
| CH50 (M ± SD) | 172.50 ± 73.42 | 190.67 ± 89.83 | 0.031 |
| C4 (M ± SD) | 16.96 ± 8.04 | 21.48 ± 9.86 | 0.024 |
| C3 (M ± SD) | 82.44 ± 39.36 | 100.12 ± 33.49 | 0.026 |

* *t* de *student* test

M = mean; DP = standard deviation; Cel p/f = cells per field; CH50 = total serum hemolytic complement; C4 = complement 4; C3 = complement 3

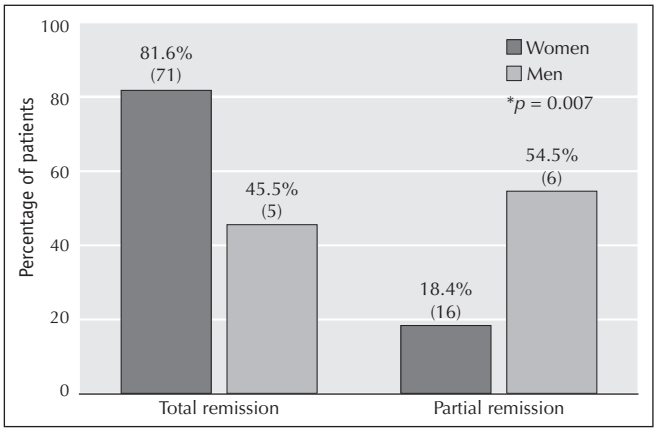
**Table 5**
Comparison among subgroups with total and partial remission at 12 months and SLE and nephritis variables at baseline: Prognostic factors.

| | Total Remission (n = 76) | Parcial Remission (n = 22) | *p |
|---|---|---|---|
| Age in years (M ± SD) | 26.57 ± 11.33 | 27.90 ± 9.04 | 0.570 |
| SLEDAI (M ± SD) | 16.17 ± 6.57 | 15.77 ± 6.47 | 0.802 |
| Creatinine in mg/dL (M ± DP) | 0.94 ± 0.86 | 1.13 ± 0.55 | 0.147 |
| Proteinuria in g/24h (M ± SD) | 2.31 ± 2.19 | 3.49 ± 2.94 | 0.093 |
| Hematuria in cel p/f (M ± SD) | 21.61 ± 22.38 | 27.77 ± 26.73 | 0.332 |
| Leucocituria in cel p/f (M ± SD) | 12.20 ± 13.35 | 22.95 ± 23.87 | 0.064 |
| CH50 (M ± SD) | 163.97 ± 119.62 | 140.75 ± 111.77 | 0.614 |
| C3 (M ± SD) | 78.39 ± 34.61 | 84.15 ± 42.68 | 0.663 |
| C4 (M ± SD) | 16.28 ± 8.63 | 16.08 ± 8.01 | 0.938 |
| Cumulative dosis of cyclophosphamide in g (M ± SD) | 9.33 ± 3.84 | 10.27 ± 4.77 | 0.42 |

* *t* de *student* test

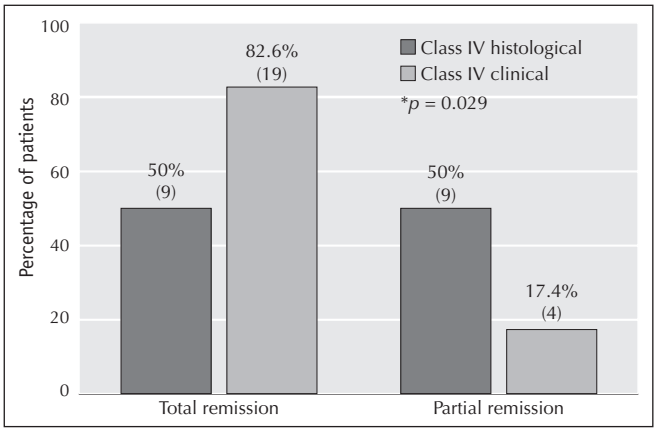
SLE = Systemic Lupus Erythematosus, M = mean, SD = standard deviation; SLEDAI = *Systemic Lupus Erythematosus Disease Activity Index*; Cel p/f = cells per field; CH50 = total serum hemolytic complement; C4 = complement 4; = C3 complement 3.

*al.*[6], patients with diffuse proliferative lupus nephritis who had received intravenous cyclophosphamide for a short period of time, followed by MMF or azathioprine maintenance therapy, demonstrate more effective results and more safety than the prolonged use of cyclophosphamide. Houssiau corroborated that IV cyclophosphamide is the only therapy able to reduce




* chi-square test

**Figure 2.** Comparison among men and women subgroups referring to total and partial remission at 12 months.




* chi-square test

**Figure 3.** Comparison among subgroups with "clinical class IV" and "histological class IV" total and partial remission at 12 months of follow-up.

**Table 6**
Comparison among "clinical class IV" and "histological class IV" subgroups

| | Class IV | | *p |
|---|---|---|---|
| | Histological (n = 18) | Clinical (n = 23) | |
| SLEDAI (M ± SD) | 16.22 ± 5.26 | 17.83 ± 5.67 | 0.356 |
| Creatinine in mg/dL (M ± SD) | 1.13 ± 0.33 | 1.09 ± 0.37 | 0.707 |
| Proteinuria in g/24h (M ± SD) | 2.67 ± 2.12 | 3.37 ± 2.70 | 0.360 |
| Hematuria in cel p/f (M ± SD) | 37.33 ± 25.22 | 34.96 ± 26.33 | 0.771 |
| Leucocituria in cel p/f (M ± SD) | 15.61 ± 12.77 | 19.78 ± 23.44 | 0.472 |
| CH50 (M ± SD) | 135.71 ± 119.62 | 124.22 ± 83.65 | 0.833 |
| C3 (M ± SD) | 86.76 ± 46.82 | 58.53 ± 19.17 | 0.117 |
| C4 (M ± SD) | 15.00 ± 6.61 | 13.07 ± 6.90 | 0.511 |
| Cumulative dosis of cyclophosphamide in g (M ± SD) | 8.72 ± 3.79 | 10.31 ± 4.48 | 0.227 |

* *t* de *student* test

M = mean, SD = standard deviation; SLEDAI = *Systemic Lupus Erythematosus Disease Activity Index*; Cel p/f = cells per field; CH50 = total serum hemolytic complement; C4 = complement 4; = C3 complement 3.

development into ESRD in these patients based in studies with long period of follow-up.[7]

Our data demonstrated satisfactory outcomes in all patients at the end of the 12-month follow-up. Among renal variables analyzed, there was a significant reduction in the 24-hour urinary protein level, improvement in the urinary sediment and increase in the fractional values of the complement ( C3, C4, CH50). The frequency of complete remission at 12 months was 72.7% and, at 24 months, 85.7% ($p$ = 0,013). According to Urowitz *et al*., patients with active lupus nephritis treated with cyclophosphamide or other immunosuppressive achieve complete remission in approximately 70% of cases.[8]

According to our data, no patient presented clinical and laboratory criteria for lack of therapeutic response by the end of 2-year of follow-up. However, these data should be carefully interpreted, since, during the study period, there was recurrence of active renal disease (flare) in approximately 40% of the patients, but after treatment optimization (increment of corticosteroids and/or immunosuppressive doses) these patients responded in a satisfactory way.

Comparison among subgroups with complete and partial remission at 12 months and the baseline variables of SLE and nephritis showed that no variable had correlation with therapeutic response. Previous studies demonstrated that variables like age, proteinuria, hematuria and arterial hypertension at diagnosis time had a questionable prognostic value in lupus nephritis outcome.[9,10,11,12] Other authors concluded in their studies that high creatinine and hypoalbuminaemia represented factors of predicting worst renal prognosis.[13,14] In a study published in Brazil,[15] it was prooved that patients with SLE onset after 16 years old, the worse outcomes had occurred in those with nephritis, revealed clinically at the beginning or in the evolution of the disease, with arterial hypertension in the beginning, with positive anti-DNA and those with cyclophosphamide use. Possible explanations for these contradictory facts derive mainly from methodological differences of the series: criteria of patient inclusion and selection, retrospective

studies, follow-up periods, treatment regimen, clinical outcome definition, sample size and others.

Male patients presented a lower rate of complete remission compared to female at 12 months, what could suggest worse prognosis of lupus nephritis among men in our population. This data differ from that in literature, where gender has no prognostic value in lupus nephritis outcome.[16]

Despite the small number of patients studied, and the controversies of renal biopsy, the rates of complete remission was higher in patients with "clinical class IV" than in those with "histological class IV" at 12 months. A balance between potential gain of information that can guide a therapeutic approach and complications associated with invasive procedure must always be considered before recommending a renal biopsy. Previous studies demonstrated that clinical and laboratory parameters are able to predict with accuracy the lupus nephritis prognosis, and biopsy is not required in every case with renal involvement.[17,18] Other studies defend that histological data provide additional information to laboratory parameters and may guide, in a more accurate way, therapeutic selection.[19] As may be noticed, this topic remains controvertial. In our experience, renal biopsy is individual and assigned, mainly, in the following situations: Question about clinical and histological correlation, presence of nephrotic syndrome or, failure to cyclophosphamide induction therapy. For this study, the frequency of complete remission at 12 months was significantly higher in patients with "clinical class IV", without the need for additional information by histological examination. In our data, renal variables and SLE, as well as cumulative cyclophosphamide doses were not different among patients with "clinical class IV" and "histological class IV", that is, with renal biopsy.

In conclusion, in this study, renal biopsy to determine the histological subtype did not influenced on therapeutic response in lupus nephritis patients during two years of follow-up. Our data demonstrated that clinical and histological correlation may help therapeutic decision of these patients, leaving renal biopsy only for special situations.

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