

Experience using low doses of calcineurin inhibitors in the treatment of refractory lupus nephritis

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Objective. To evaluate the effectiveness of calcineurin ciclosporin and tacrolimus inhibitors to induce remission in patients with refractory lupus nephritis.

Patients, materials and methods. Patients with lupus nephritis class IV-G who despite receiving therapy with high doses of steroid and with a cytostatic (cyclophosphamide or mycophenolate) for 3 months had not been able to induce some kind of remission. The exclusion criteria were creatinine levels greater than 3 mg / dl, pregnancy, previous history of exposure to calcineurin inhibitors, cancer, active infections, uncontrolled hypertension, and negligence with medication intake.

The recommended dose of cyclosporine was 3 mg / kg / day and tacrolimus 0.1 mg / kg / day, in joint with prednisone 0.3 mg / kg / day, cyclophosphamide 1 mg / kg / day or mycophenolate mofetil 1 gram every 12 hours. The cyclophosphamide was administered only during 6 months, after which it was changed to azathioprine at doses of 1 mg / kg / day. Still, mycophenolate was continued at the same dose.

All patients completed a minimum period of 12 months follow-up, it was considered that patients achieved partial remission when proteinuria decreased by 50% of the baseline value or its value decreased to less than 1 gram in 24 hours, decrease of leukocytes count and red blood cells in urine of 50%, and creatinine values were stable. A complete remission was considered when there was a reduction in proteinuria in a value less than 300 mg per 24 hours, urinary sediment with less than 3 red blood cells, less than 5 leukocyte for each high power microscopic field, and a creatinine value reduction by 50% or reaching a normal value.

Results. Twelve patients met the inclusion criteria and initiated the calcineurin inhibitor protocol. Two presented accelerated deterioration in their function and required chronic dialysis therapy. Ten patients with active treatment completed 12 months of follow-up, of which 4 (40%) had partial remission (PR), 5 (50%) complete remission (RC). One patient had no significant modification to his baseline values.

The following findings were made for all the patients with any significant degree of remission: their creatinine levels were reduced significantly from an average value of 1,34 +/- 0,7 mg/dl to an average of 0,96 +/- 0,3 mg/dl and 0,97 +/- 0,24 mg/dl for measurements taken 6 and 12 months respectively after the start of the treatment ($p < 0,05$). The protein levels in the urine in a timeframe of 24 hours changed from a baseline value of 2865 +/- 2586.7 milligrams to 824 +/- 981.9 milligrams at 6 months, and 488 +/- 697.7 milligrams at 12 months ($p < 0,05$). On average, in both PR and CR patients, the C3 levels raised unlike the values for antinuclear antibodies that were diminished. No patients died, nor were there significant side effects triggered by medications. No patient presented relapses during the follow-up time.

Conclusion. The calcineurin inhibitors at low doses are an important alternative to induce partial or complete remission in patients with refractory lupus nephritis compared to classic steroid and cytostatic treatment. It is required to do a long-term follow-up to establish its safety profile at low doses and relapse rate after suspension.

Keywords. Lupus nephritis, cyclosporine, tacrolimus.

Experiencia en la utilización de inhibidores de calcineurina a bajas dosis en el tratamiento de nefritis lúpica refractaria

RESUMEN

Objetivo: evaluar la efectividad de los inhibidores de calcineurina ciclosporina y tacrolimus para inducir remisión en pacientes con nefritis lúpica refractaria.

Pacientes, materiales y métodos: pacientes con nefritis lúpica clase IV-G quienes a pesar de recibir terapia con esteroides a altas dosis y un citostático (ciclofosfamida o micofenolato) por 3 meses no se había logrado inducir algún tipo de remisión.

Fueron criterios de exclusión creatinina mayor a 3 mg/dl, embarazo, antecedentes de exposición previa a inhibidores de calcineurina, cáncer, infección activa, hipertensión no controlada y no colaboración con la toma de medicamentos. La dosis elegida de ciclosporina fue 3 mg/kg/día y de tacrolimus 0,1 mg/kg/día, asociados a prednisona 0,3 mg/kg/día, ciclofosfamida 1 mg/kg/día o micofenolato mofetilo 1 gramo cada 12 horas. La ciclofosfamida se administró solo por 6 meses, posteriores a los cuales fue cambiada a azatioprina a dosis de 1 mg/kg/día, el micofenolato se continuó a igual dosis.

Todos los pacientes completaron un mínimo de 12 meses de seguimiento, se consideró que los pacientes lograron remisión parcial cuando la proteinuria disminuyó en 50% del valor inicial o su valor se redujo a menos de 1 gramo en 24 horas, disminución de leucocitos y glóbulos rojos en orina en 50% y estabilización de la creatinina; remisión completa se definió por reducción en la proteinuria a un valor menor a 300 mg por 24 horas, sedimento urinario con hematíes menos de 3, leucocitos menos de 5 por campo de alto poder y reducción de la creatinina en un 50% o alcanzando un valor normal.

Resultados: doce pacientes cumplieron con los criterios de inclusión e iniciaron el protocolo de inhibidores de calcineurina. Dos presentaron deterioro acelerado en la función y requirieron terapia dialítica crónica. Diez pacientes con tratamiento activo completaron 12 meses de seguimiento, de ellos 4 (40%) lograron remisión parcial (RP), 5 (50%) remisión completa (RC) y en un paciente no se modificaron significativamente los valores iniciales. En el total de pacientes con alguna forma de remisión la creatinina disminuyó significativamente en promedio, de un valor de 1.34 +/-0.7 mg/dl a 0.96 +/- 0.3 mg/dl y 0.97 +/- 0.24 mg/dl a los 6 y 12 meses, respectivamente ($p<0,05$). Los niveles de proteínas en orina de 24 horas en el total de pacientes cambiaron de un valor inicial de 2865 +/- 2586,7 miligramos a 824 +/- 981,9 miligramos a los 6 meses y 488 +/- 697,7 miligramos a los 12 meses ($p<0,05$). En promedio tanto en los pacientes con RP como RC los niveles de C3 se elevaron y los de anticuerpos antinucleares disminuyeron significativamente. Ningún paciente falleció, ni se presentaron efectos colaterales importantes desencadenados por los medicamentos.

Ningún paciente presentó recaídas durante el tiempo de seguimiento.

Conclusión: los inhibidores de calcineurina a bajas dosis son una alternativa importante para inducir remisión parcial o completa, en pacientes con nefritis lúpica refractaria, al tratamiento clásico con esteroides y citostáticos. Se requiere seguimiento a largo plazo para establecer su perfil de seguridad a dosis bajas y tasa de recaídas post-suspensión.

Palabras clave: nefritis lúpica, ciclosporina, tacrolimus.

Introduction

Lupus nephritis occurs in 60% of patients with systemic lupus erythematosus (SLE)¹. Abnormal urinary sediment with or without elevated values of creatinine is present in 50% of patients at the moment of diagnosis. An alteration in the renal functions develops over time in more than 75% of patients, causing major impact on their lifetime².

In patients with LN class IV, aggressive immunosuppressive therapy has been recommended since the risk of progression to chronic kidney disease (CKD) stage 5 is high. The guidelines to inducing remission form a LN always include steroids because of their strong inflammatory performance, while cytostatics provide better long-term control by generating sustained immunosuppression. This way preservation and relapse of the renal function is avoided. Thus, the combination of steroid and cytostatic is superior to steroids itself in the prevention of chronic kidney damage³⁻⁵.

Among the cytostatics, the cyclophosphamide has been classically used in various schemes to induce remission, although it has recently been suggested that mycophenolate could be just as beneficial⁶. Nearly 20% of the patients do not respond to steroid + cytostatic association⁷⁻¹⁰ and are considered to have refractory LN with a high chance of progression to a chronic kidney disease. In this last group, several therapeutic alternatives have been proposed, and the purpose of this study is to report our experience in the use of calcineurin inhibitors in patients with refractory LN with continuous monitoring during 12 months.

Patient materials and methods

Patients had SLE and were consulted by the Department of internal medicine, nephrology sessions, and health sciences of the University of Caldas, because they presented lupus nephritis refracting to classic treatment and had been treated by internists or rheumatologists for a minimum period of 3 months.

The inclusion criteria to participate in the study were: diagnosis of SLE according to the revised criteria of the Colegio Americano de Reumatología¹¹, lupus nephritis LN class IV-G (diagnosed by renal biopsy not higher than 3 months before initiating the protocol), according to the criteria of the International Society of Nephrology¹², ages older than 18 years and younger than 80 (for ages under 18 years only under parental authorization), with absence of active infection or neoplasm, and that have received induction with steroid associated to a cytostatic for a 3 months period without a satisfactory response. The steroid administered by internists or rheumatologists was methylprednisolone in pulses of 30 mg / kg / day (maximum dose 1 gram) during 3 days followed by an oral dose of 1 mg / kg / day of prednisone. The cytostatics used were cyclophosphamide 500 mg IV biweekly for a total of 6 doses, or 500 to 1000 mg / mt2 every month for a total of 3 doses, followed by a dose of 1 mg / kg / day, orally, for a maximum of 6 months. The mycophenolate mofetil was administered at a dose of 1 gram given orally every 12 hours regardless of body weight. We also included patients with the above criteria who, despite administering 375 mg / mt2 intravenous rituximab, 4 doses, had unsatisfactory results.

The exclusion criteria were: creatinine values greater than 3 mg / dl, pregnancy, previous history of exposure to calcineurin inhibitors, cancer, active infection, uncontrolled hypertension and negligence with medication intake.

Depending on the characteristics of the patients, all patients received a daily dose of cyclosporin of 3 mg / kg according to the body weight divided in two doses administered every 12 hours; or tacrolimus at a dose of 0.1 mg / kg / day, with prednisone at 0.3 mg / kg / Day, and cyclophosphamide 1 mg / kg / day; or mycophenolate mofetil 1 gram, every 12 hours.

Every month, during 6 months and then every 2 to 3 months, a complete blood count was evaluated along with creatinine values, Bun, urine test, creatinine clearance, and protein in urine for 24 hour period. Each semester (every 6 months) C3, C4, ANAS, and native AntiDNA was checked. Cyclosporine or tacrolimus levels were not evaluated because the do-

ses administered were lower than those usually used in aggressive immunosuppression protocols.

Patients achieved a partial remission when within the 12 month period of follow-up proteinuria levels decreased by 50% from baseline values, or its total value decreased to less than 1 gram in 24 hours; and a reduction in leukocytes count and red blood cells in urine by 50%, and stable creatinine values. A complete remission was defined when there was a reduction in proteinuria values lower than 300 mg in a 24 hours period, red blood cells values less than 3 and leukocytes less than 5 per field of high power in urine sediments, and reduction of creatinine values by 50%, or reaching normal values.

In addition, relapses were recorded. It was criteria for diagnosis the following: recurrence of nephrotic syndrome, decrease in glomerular filtration rate with increase in creatinine values by 30%, and presence of active sediment with hematuria and leukocyturia. Patients kept the dose of ciclosporin for at least 1 year without changes, making it possible to reduce the dose of prednisone to 0.15 mg / kg / day every other day. The cyclophosphamide was administered for 6 months, and was then changed to azathioprine at a dose of 1 mg / kg / day keeping it this way throughout the study. The dose could be reduced according to the white blood cell count. The dose of mycophenolate did not change throughout the year of administration, except in cases of medullary depression. Triple therapy was considered refractory when, after 5 months of administration or during the course of the therapy, there was a continuous increase in creatinine; persistence or worsening of proteinuria; and active urinary sediment, in which case, if there were no contraindications, it was proceeded with the use of rituximab or plasmapheresis.

To perform the analysis of the data was used the program SPSS version 15.0. A description of measures of central tendency and of dispersion was realized initially. The effects of the treatment were evaluated by a Variance Analysis of Repeated Measures in the group of study, at different times of the time, applying a linear model, and making an adjustment for multiple comparisons: Bonferroni.

Results

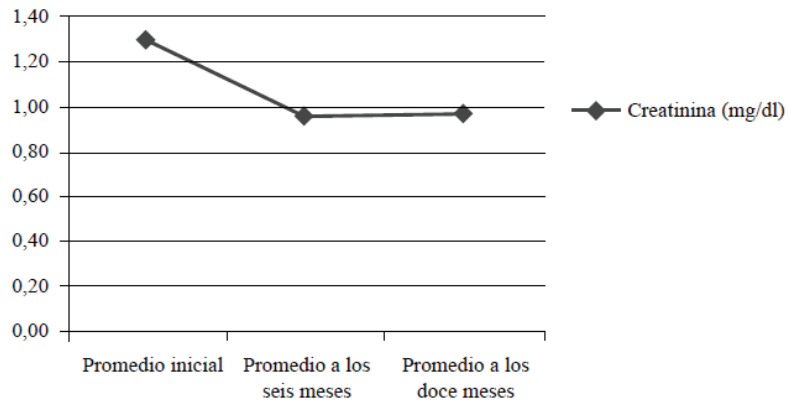
During 10 years, 12 patients met the inclusion criteria and were submitted to a therapy with calcineurin inhibitors. Two female patients presented accelerated deterioration in renal function despite the initiation of the calcineurin inhibitor (one with tacrolimus and the other with cyclosporine, both receiving cyclophosphamide). In one it was administered 4 doses of rituximab each week, and in the other a plasmapheresis scheme. Therapeutic benefit was not achieved, requiring chronic dialysis therapy. Ten patients completed the minimum requirement of 12 months of follow-up after initiating the calcineurin inhibitor. The average age of patients was 22.7 +/- 12.9 years; 8 women and 2 men; all Latinos. Only 2 patients received tacrolimus and 3 mycophenolate; the rest were treated with cyclosporine, cyclophosphamide, and had azathioprine as upkeep.

Four patients (40%) achieved partial remission (RP) and 5 (50%) complete remission (RC); in 1 patient (10%) proteinuria persisted at a value greater than 2 grams for a period of 24 hours, close to baseline value, without deteriorating its glomerular filtration rate (GFR). This patient was treated with tacrolimus and mycophenolate. Plasma creatinine decreased in the complete group of patients from 1.34 +/- 0.7 mg / dl to 0.96 +/- 0.3 mg / dl and 0.97 +/- 0.24 mg / dl at 6 and 12 months, respectively, without significant variations in the groups with RP and CR.

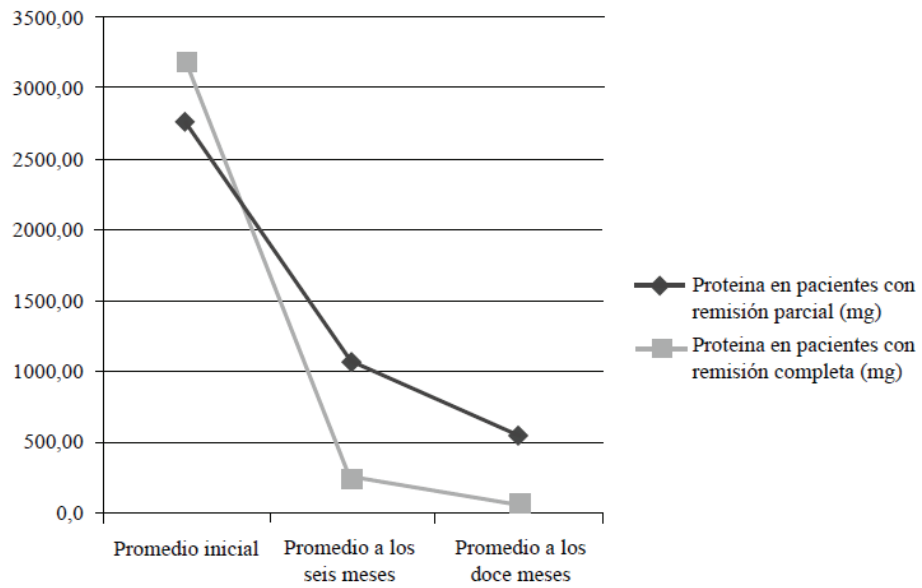
The urinary protein levels in a lapse of 24 hours in the total number of patients changed from an initial value of 2865 +/- 2586.7 milligrams to 824 +/- 981.9 milligrams at 6 months and 488 +/- 697, 7 milligrams at 12 months. Whereas, in the analysis of groups, patients with partial remission had proteinuria from an initial value of 2757 +/- 1223.6 milligrams to 1075 +/- 979.7 milligrams at 6 months, and 551 +/- 265.2 milligrams at 12 months. In the group of patients with complete remission, the proteinuria evolved from 3165 +/- 3677.5 milligrams to 249 +/- 305.6 milligrams at 6 months and 75 +/- 66.9 milligrams at 12 months.

Complement values were significantly elevated in both RP and RC patients. In general, the C3 changed

GRAPH 1. AVERAGES BEHAVIOR: C3 AND C4.



GRAPH 2. AVERAGE BEHAVIOR: RED BLOOD CELLS AND LEUKOCYTES



from 51.9 +/- 22.7 mg / dl to 113.6 +/- 38.8 mg / dl and 125.7 +/- 36.2 mg / dl, while the C4 11.2 +/- 7.0 mg / dl at 36 +/- 43.4 mg / dl and 59.46 +/- 63 mg / dl at 6 and 12 months, respectively. The behavior of red cells count was always downward in the 3 measurements as follows: 15 +/- 9.5 per field of high power to 5.4 +/- 5.3 and 1.1 +/- 2.2, and the count of leukocytes had a similar behavior of 14.7 +/- 11.2 per high power field at 2.4 +/- 2.9 and 1.4 +/- 0.7, respectively (Table 1).

Antinuclear antibody titers decreased in both groups and globally from 1: 402 to 1: 140 and 1:60, respectively, in the periods previously noted. There were not sufficient native anti-DNA titres obtained for statistical analysis.

No patient had relapse during the follow-up period in the active treatment phase using calcineurin inhibitors.

There were no significant side effects that made imperial the discontinuation of calcineurin inhibitors. No patient died within the 12 months of follow-up period or presented evidence of extra renal lupus activity.

In the statistical analysis for the variable that measures protein and creatinine in urine during 24 hours

measured in the 10 patients, the results showed that there are significant statistical differences $P < 0.05$. No statistical significant differences were found for the protein measured in patients who achieved complete remission, nor in the values measured for C4 (Table 2).

When analyzing the behavior of C3 the ANOVA result when applying the linear model for repeated measures, indicates that there are statistically significant differences between the 3 levels of the variable. When comparing the possible pairs it is confirmed the relation between all, except in the measurement of the second with the third and the third with the second, $p < 0.000$ (Table 2).

When analyzing the behavior of red blood cells count, evidence shows that there were statistically significant differences between the subjects even when comparing each of the pairs analyzed $p < 0.000$.

The behavior of the leukocytes, when comparing the first measurement with the intermediate and the last one, was statistically significant. The same was found when comparing the second measurement with the first and the third with the first. The intra-subject evaluation was statistically significant at $p < 0.000$.

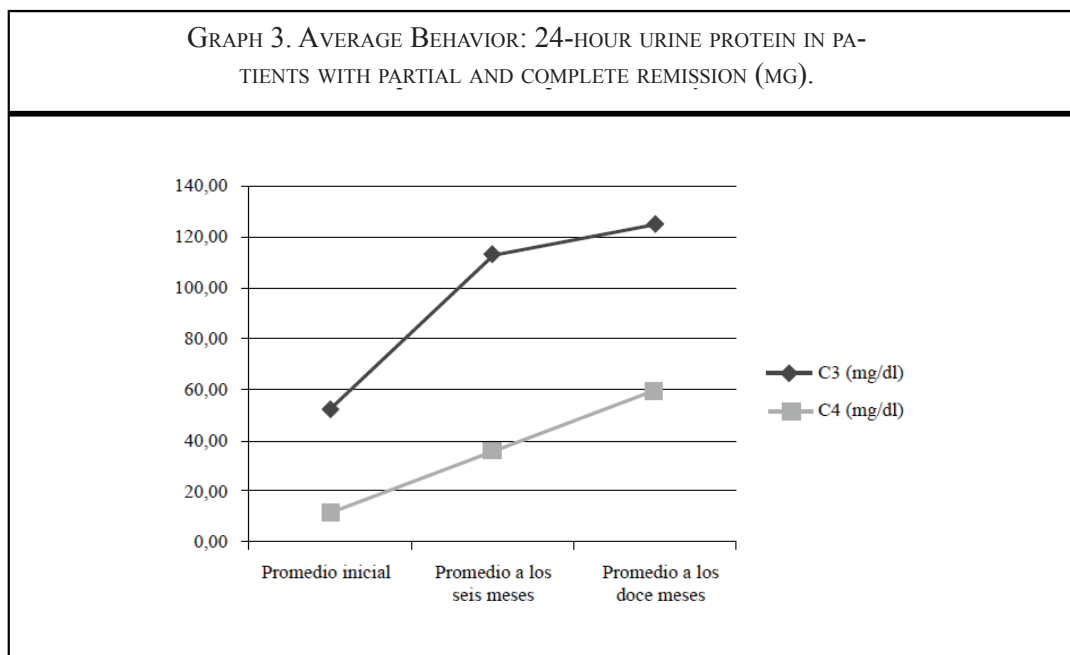


TABLE 1 DESCRIPTIVE STATISTICS

| Variable | N | Min | Max | Mean | Typical Dev |
|---|----|-------|-------|--------|-------------|
| Age (years) | 10 | 13 | 55 | 22.7 | 12.9 |
| Initial Creatinine (mg/dl) | 10 | 0.6 | 2.5 | 1.3 | 0.7 |
| Creatinine 6 months (mg / dl) | 10 | 0.6 | 1.7 | 0.9 | 0.3 |
| Creatinine 12 months (mg/dl) | 10 | 0.7 | 1.38 | 0.97 | 0.24 |
| Initial 24-hour urine protein (mg) | 10 | 540 | 9016 | 2865.6 | 2586.6 |
| Protein in urine for 24 hours six months (mg) | 10 | 67 | 2700 | 824.5 | 98.8 |
| 24-hour urine protein 12 months (mg) | 10 | 10.0 | 2300 | 488 | 697.7 |
| 24-hour urine protein initial partial remission (mg) | 4 | 990 | 3790 | 2757.5 | 1223.5 |
| 24-hour urine protein partial remission 6 months (mg) | 4 | 280 | 2392 | 1075 | 979.7 |
| 24-hour urine protein partial remission 12 months (mg) | 4 | 330 | 928 | 551.2 | 265.2 |
| 24-hour urine protein initial complete remission (mg) | 5 | 540 | 9016 | 3165.2 | 3677.5 |
| 24-hour urine protein complete remission 6 months (mg) | 5 | 67 | 788.8 | 249.1 | 305.6 |
| Proteína en orina de 24 horas remisión completa 12 meses (mg) | 5 | 10 | 174.2 | 75 | 66.9 |
| C3 initial (mg/dl) | 10 | 25 | 90 | 51.9 | 22.7 |
| C3 6 months(mg/dl) | 10 | 47 | 170 | 113.6 | 38.8 |
| C3 12 months (mg/dl) | 10 | 87.9 | 189 | 125.7 | 36.2 |
| C4 initial (mg/dl) | 10 | 4 | 24.6 | 11.1 | 7 |
| C4 6 months (mg/dl) | 9 | 7.3 | 150 | 36 | 43.4 |
| C4 12 months (mg/dl) | 9 | 18.4 | 221 | 59.5 | 63 |
| ANA initial | 10 | 1: 80 | 1:640 | 1:403 | 1:214 |
| ANA 6 months | 9 | 1:40 | 1:398 | 1:141 | 1:115 |
| ANA 12 months | 8 | 1:20 | 1:160 | 1:60 | 1:47 |
| Red blood cells initial (# per field of high power) | 10 | 3 | 35 | 15 | 9.6 |
| Red blood cells 6 months (# per field aof high power) | 10 | 1 | 18 | 5.4 | 5.4 |
| Red blood cells 12 months (# per field of high power) | 10 | 0 | 7 | 1.1 | 2.2 |
| Initial urine leukocytes (# by high power field) | 10 | 3 | 38 | 14.7 | 11.2 |
| Leukocytes 6 months (# per field of high power) | 10 | 1 | 9 | 2.4 | 2.9 |
| Leukocytes 12 months (# per field of high power) | 10 | 1 | 3 | 1.4 | 0.69 |

The ANA showed a statistically significant difference for the relation between the subjects and when comparing the first and third evaluation $p < 0.002$.

In the patients that had complete remission there were no evidence of significant statistical values of protein, compared to patients who achieved partial remission in which the value for p intrasubjects was of 0.014.

Discussion

The induction of remission in patients with lupus nephritis is the main goal pursued by every nephrologist when treating this group of patients. Classically, the regimen of cytostatic associated with steroid is recommended. Steroids are generally used in daily intravenous pulse forms for 3 days, followed by high

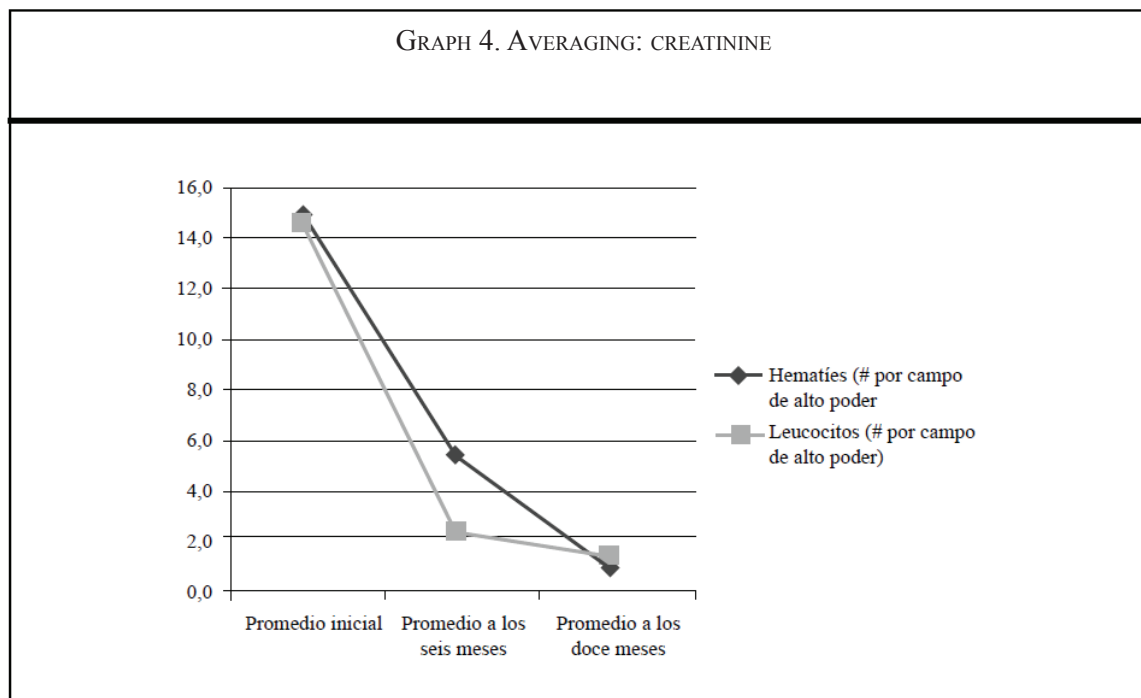


TABLE 2 BEHAVIOR OF THE STUDIED VARIABLES AVERAGES AND P VALUE.

| Variable | Promedio inicial | Promedio a los 6 meses | Promedio a los 12 meses | Valor de p.(*) |
|---|------------------|------------------------|-------------------------|----------------|
| Age (years) | 22.7 | | | |
| Creatinine (mg/dl) | 1.3 | 0.96 | 0.97 | 0.02 |
| 24-hour urine protein (mg) | 2865.6 | 824.5 | 488 | 0.007 |
| Proteins in patients with partial remission (mg) | 2757.5 | 1075 | 551.3 | 0.014 |
| Proteins in patients with complete remission (mg) | 3165.2 | 249.1 | 75.04 | 0.076 |
| C3 (mg/dl) | 51.9 | 113.6 | 125.7 | 0.0000 |
| C4 (mg/dl) | 11.2 | 36 | 59.4 | 0.070 |
| ANAS | 402.9 | 140.9 | 60 | 0.002 |
| Urine Red Blood Cells (# by high power field) | 15 | 5.4 | 1.0 | 0.000 |
| Leukocytes in urine (# by high power field) | 14.7 | 2.4 | 1.4 | 0.000 |

(*)It corresponds to the comparison of the average values at the beginning, at 6 months, and at 12 months

oral doses. Among the cytostatics diverse schemes has been used to induce remission with cyclophosphamide, from oral administration to intravenous preparations in monthly doses of 500 to 1000 mg / mt², at low doses (500 mg) every 15 days for 6 doses (Euro-Lupus regimen)¹³. The mycophenolate, to date, also represents an excellent option to induce remission, mainly in Latinos, Afro-descendants and young individuals in whom it is desired to preserve the gonadal function¹⁴. However, there is a group of patients in whom, despite the administration of a classic induction regimen, it is not possible to obtain a good therapeutic response in the course of 3 months, being considered as having refractory lupus nephritis. In the latter group of patients, several therapeutic regimens have been proposed, which include the additional prescription of: monoclonal antibodies to CD 20 (rituximab), intravenous gammaglobulin, plasmapheresis and immunoabsorption, immunoablative therapies, tumor necrosis factor alpha antagonists and, finally, calcineurin inhibitors.

The timeframe with which therapeutic refractoriness has traditionally been defined for lupus nephropathy has been 6 months. We chose one of 3 months because the class IV-G variety of lupus nephritis is a very aggressive entity and the absence of response in only 3 months can generate severe and irreversible side effects. Regard this matter, recent publications agree with this concept and suggest very clearly that if a patient during the first 3 months of steroid treatment associated with cytostatic experiences aggravation in their clinical and laboratory records, it is imperative to initiate or add an alternative therapy¹⁵⁻¹⁷.

Several studies have demonstrated the importance of T cells in the pathogenesis of SLE^{18,19}. Calcineurin inhibitors (cyclosporin and tacrolimus) are drugs with a powerful inhibitory effect on the clonal expansion of helper T cells and cytotoxic T cell function, through the decrease in the synthesis of IL-2, IL-3 and IFN- Alpha, a mechanism by which they could achieve therapeutic benefits in lupus nephritis. One of the problems of administration of calcineurin inhibitors is its toxicity profile: nephrotoxicity, hypertension, hypertrichosis, hyperuricemia, diabetes mellitus and hyperlipidemia, mainly, when used in the long term and in high doses (3.5 to 5 mg / Kg /

day). Lower doses between 2 to 3 mg / kg / day may keep their activity and generate less side effects.

The experience of the use of cyclosporine, at high doses, in refractory lupus nephropathy class IV is scarce and in a limited number of patients. Favre et al., in 18 patients²⁰, Rihova et al., in 13 patients²¹, Tam et al., in 17 patients²², Ferrario L. et al., in 3 patients²³, Manger et al., in 10 patients²⁴ and Tokuda et al in 10 patients²⁵; they prescribed ciclosporin doses ranging from 3.0 to 5.0 mg / kg / day in patients with refractory lupus nephritis, achieving good clinical response, reduction in proteinuria, and stabilization in renal function. But the long-term results with the amount of doses administered are unknown, in which side effects are more likely to occur.

Reports of patients with refractory lupus nephritis class IV treated with low doses of calcineurin inhibitors are few, which explains also the low sample that we managed to collect in the course of 10 years of being consulted by this type of pathology. Caccavo et al., in Italy, intervene 30 patients with refractory SLE (without indication of how many with refractory lupus nephritis), which were treated with ciclosporin at doses of 2.5-3.5 mg / kg / day. In a 24 months period of follow-up they decreased the score of systemic lupus activity (SLAM), and in the group of proteinuric patients reduction in proteinuria and stabilization in renal function was observed. There was also a reduction in native anti-DNA antibody titers, fluctuation in the values of ANAS and increased values of C3 and C4²⁶. Ogawa H. et al., treated 51 Japanese patients with refractory SLE. 26 had lupus nephritis and 18 of them were treated with cyclosporine at an initial dose of 2.5 mg / kg / day, adjusting doses according to serum levels, achieving RC in 6 Patients, PR in 5, absence of response in 1, and suspension of the drug in 4 due to renal impairment. The levels of native anti-DNA antibodies decreased and CH50 titers increased in the response groups. ²⁷ Ogawa H et al., also in Japan, throw results of low doses of cyclosporine (2.5 mg / kg / day) in 9 patients with refractory lupus nephritis who underwent 30 weeks of treatment with satisfactory results in 70%. In this study there were no significant modifications in the CH50 and nor in anti-DNA antibodies²⁸. Baca et al., in Mexico, reported results

of experiment in 7 children with Class III and IV varieties refractory to cytostatic with steroids, and treated with low doses of cyclosporine (2 to 4 mg / kg / day). It showed good results during the time, but most patients relapsed with the presence of proteinuria once cyclosporine was suspended²⁹.

There are reports of treatment with another calcineurin inhibitor, the tacrolimus, in patients with refractory lupus nephropathy. In a case study of a patient with lupus nephropathy class IV who required renal replacement therapy complete remission of nephropathy is reported after 7 months of treatment³⁰. In another report, the experience with 3 patients and a positive response in 2 of them at 6 and 9 months of treatment respectively, it's notified³¹. Uchino et al., at Japan, intervened 23 patients with refractory lupus nephritis who were treated with steroid associated with tacrolimus ranging from 2 to 3 mg per day during 6 months and without cytostatic. 22 patients completed the follow-up time and in them he observed a significant reduction of proteinuria and improvement in urinary sediment. The levels of fats were not significantly modified, whereas those of CH50 and C3 were elevated in the 6 month period of follow-up³². Fei Y. et al., in China, intervened 26 patients with lupus nephritis refractory to cyclophosphamide associated with steroids. They used a tacrolimus dose ranging from 2 to 3 mg / day and found in a 6 month period of follow-up partial or complete response in 88.46% of the patients³³. Similar results were reported by Gordon S. et al., in 8 female patients with refractory lupus nephritis to mycophenolate and steroids, treated with an average dose of tacrolimus of 3.3 mg / day for approximately 16 months³⁴.

There are reports of patients with non-refractory lupus nephritis treated with calcineurin inhibitors, for the main purpose of inducing first instance remission or sustained remissions. Although there is literature

on this subject, this is not the target of the paper, therefore, we do not deepen into the subject³⁵⁻³⁷.

In addition to the nephrotoxicity profile of calcineurin inhibitors at high doses and a long period of time, a problem that has been detected with its administration is the high rate of relapse after withdrawal. In the Rihova study, values close to 46% were reported²¹, resulting in a group of patients dependent on cyclosporine. It is also important to note that due to the risk of worsening renal function, it is recommended to avoid cyclosporin when the glomerular filtration rate is lower than 60 ml / minute and the renal biopsy shows severe tubulointerstitial fibrosis. A therapeutic alternative in patients with high activity rates, but with GFR greater than 60 ml / minute, cyclosporine could be used initially at a dose of 5 mg / kg / day, and slowly and carefully reduce it to a keeping dose of 2 to 3 Mg / kg / day. If creatinine is increased by 30% during the follow-up period, reduce the dose by 25%, but if values rises by 50% temporarily, suspend it and restart at 2 to 4 weeks with low doses. A further elevation of creatinine should lead to its definitive suspension. In some situations it is difficult to establish whether the elevation of azoles is the result of lupus activity or toxicity by cyclosporine. In these cases the determination of high levels of native AntiDNA, anti-C1q and low C3 and C4 antibodies would be compatible with active lupus nephritis, although in special cases a new renal biopsy may be required.

To conclude, in our study, with a limited number of patients, evidence shows that calcineurin inhibitors, mainly cyclosporin at low doses (2 to 3 mg / kg / day) are useful in inducing complete or partial remission in patients with refractory nephritis Lupus to steroids and cytostatics. Only with a long-term period analisis will it be possible to establish its safety profile at low doses, and relapse rate after suspension.

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