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Mycophenolate Mofetil in the treatment of Lupus Nephritis, in patients with failure, intolerance or relapses after treatment with steroids and cyclophosphamide

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SUMMARY

Intravenous cyclophosphamide (IVCP) in combination with oral steroids (ST) is the most widely accepted therapy for severe lupus nephritis (LN); however, its side effects, lack of response and relapses, have led to other treatment alternatives. being sought. Mycophenolate mofetil (MMF) has been shown to be effective in these cases. We studied the course over 12 months of 28 patients with LN WHO class III (n = 3), IV (n = 22) or V (n = 3), with 38,1 ± 11,4 tears of age, proteinuria 4,2 ± 2,6g /24 hours and serum creatinine 1,4 ± 0,8 mg/dL, who, after being initially treated with ST and IVCP, showed no response (n = 21), frequent relapses (n = 6), or adverse side effects (n = 1). All patients were treated with MMF in doses of 1,000 to 2,000 mg/day combined with ST or cyclosporine for one year. Four patients withdrew from treatment before the end of the follow-up. None of the patients who completed the study showed changes in hematologic parameters. Creatinine and creatinine clearance remained stable. Resulted in a significant improvement; serum albumine (3 ± 0,8 vs *3,9 ± 0,5 g/dL) p < 0.01, and decreased of proteinuria (4,2 ± 2,6* vs *1,8 ± 2,2 g/ 24 hours) p < 0.05, complement fractions improvement significantly, C3 and CH50 p < 0.05, C4 p < 0.01. Antinuclear antibodies (ANA) and anti-DNA antibodies decreased significantly (p < 0.05). During follow-up, a reduction in the ST dose was achieved: 18.3 ± 10,5* vs *10,1 ± 4,1 mg/24 h (p < 0.01). Three mild side effects related to MMF were observed and only 1 case required discontinuation of treatment. We concluded that MMF is a useful drug in the treatment and control of lupus nephritis, which also allows for a significant reduction in the dose of ST, with minimal side effects.*

Key words: ***Systemic lupus erythematosus. Lupus nephritis. Mycophenolate mofetil. Steroids. Cyclophosphamide.***

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MICOFENOLATO MOFETI EN EL TRATAMIENTO DE LA NEFRITIS LÚPICA EN PACIENTES CON FRACASO, INTOLERANCIA O RECIDIVAS TRAS TRATAMIENTO CON ESTEROIDES Y CICLOFOSFAMIDA

RESUMEN

La asociación de Esteroides orales y Ciclofosfamida intravenosa en bolos, es la pauta terapéutica más aceptada en la Nefritis Lúpica severa. Los efectos secundarios, así como los casos de falta de respuesta y recidivas han hecho que se busquen otras alternativas terapéuticas. El Micofenolato Mofetil se ha mostrado eficaz en estos casos. Hemos estudiado la evolución, a lo largo de 12 meses, de 28 pacientes afectos de Nefritis Lúpica clase III (n = 3), IV (n = 22) y V (n = 3), según la clasificación de la Organización Mundial de la Salud, con edad de 38,1 ± 11,4 años, todos presentaban proteinuria y en la mitad de ellos era mayor de 3,5 g/24 horas, la creatinina sérica fue 1,4 ± 0,8 mg/dL. Habiendo sido tratados inicialmente con esteroides y Ciclofosfamida intravenosa en bolos, habían presentado falta de respuesta (n = 21), recidivas frecuentes (n = 6), o efectos secundarios adversos (n = 1). Todos ellos han sido tratados, durante 12 meses, con Micofenolato Mofetil con dosis de 1.000 a 2.000 mg/día asociado a esteroides o Ciclosporina durante un año. Cuatro pacientes abandonaron el tratamiento antes de finalizar el periodo. Observamos incremento de albúmina sérica 3 ± 0,8 vs *3,9 ± 0,5 g/dL), p < 0.01 descenso de la proteinuria en 24 horas (4,2 ± 2,6* vs *1,8 ± 2,2 g) p < 0.05. Las fracciones del complemento mejoraron. C3 y CH50 p < 0.05. C4 p < 0.01. Los Anticuerpos anti nucleares y los anticuerpos anti DNA descendieron de forma significativa (p < 0.05). A lo largo del seguimiento se logro una reducción de la dosis de esteroides: 18,3 ± 10,5* vs *10,1 ± 4,1 mg/24 h (p < 0,01). Se observaron 3 acontecimientos adversos leves relacionados con el MMF y solo 1 caso precisó suspensión del tratamiento. Concluimos que el Micofenolato Mofetil es un fármaco útil en el tratamiento y control de la Nefritis Lúpica, y permite además una reducción significativa de la dosis de esteroides, con mínimos efectos secundarios.*

Palabras clave: ***Lupus eritematoso sistémico. Nefritis lúpica. Micofenolato mofetil. Esteroides. Ciclofosfamida.***

INTRODUCTION

Systemic lupus erythematous (SLE) is an autoimmune disease in which T and B lymphocytes function is impaired, although the pathogenic mechanisms remain unknown.

Renal involvement occurs in 60% of the cases and represents one prognostic factor of the disease.[1] Among the different types of lupus nephritis (LN), the so-called class IV of World Health Organization (WHO) classification is the most sever one. In the last decades different therapeutic regimens have been proposed, the association corticosteroids cyclophosphamide being the one showing the best results,[2,3] especially when the therapy is started early.[4] However, this regimen also has important side effects, so that its usefulness is time and dose limited.[5,6]

Mycofenolate mofetil (MMF) is an important inmunosupresor of T and B lymphocytes proliferation. Its active form is mycofenolic acid that acts in a noncompetitive and reversible way inhibiting inosine mono phosphate dehydrogenase. Although its initial indication was as an immunosuppressant to prevent transplant rejection, there are currently multiple indications within the filed of autoimmune diseases.[7,8]

A recent meta-analysis carried out by Flanc *et al.* concludes that the association cyclophosphamide (CP) and steroids (ST) represents the best option to preserve renal function in patients with diffuse proliferative LN;[9] in spite of that there is a percentage of patients in whom, for several reasons, among which ethnicity has been implicated, the above-mentioned therapy is not effective,[10] which leads us to seek for other therapeutic alternatives.

In recent years, several references have been done to the therapeutic usefulness of MMF in lupus nephritis and other manifestations of the disease,[11-13] both in animal models[14,15] and humans, with few side effects.[5,10,16]

MATERIAL AND METHODS

An observational multicenter prospective study has been done including 28 patients: 23 women and 5 men diagnosed with SLE according to the American Rheumatism Association criteria.

All had renal biopsy taken that was assessed by light microscopy and immunofluorescence, being diagnosed with lupus nephropathy according the WHO-based classification.[17] Three patients had class III LN, 22 class IV, and 3 class V. Twenty-three patients had received previous therapy with oral prednisone (PRD) and intravenous cyclophosphamide (IVCP), and 5 had been treated with cyclosporin. They were included into the study according to the following criteria: 21 (75%) due to lack of therapeutic response, defined as no decrease of proteinuria and increase of serum creatinine. Six (21.4%) patients had frequent recurrences in spite of treatment, and patients still presented relapses of lupus activity. One (3.6%) patient had side effects attributable to cyclophosphamide. All patients expressed their written informed consent to be treated with MMF associated to prednisone or cyclosporin (CSA).

Patients were followed up at weekly intervals during the first month, monthly for the following 3 months, and quarterly thereafter until completing 12 months, at which time the study was concluded. All women had a pregnancy test performed every month.

Patients followed different therapeutic regimens; all had MMF added to their previous regimen before being included into the study. In this way, 21 received ST plus MMF, 5 cyclosporin plus MMF, and two cases had their previous therapy withdrawn and received MMF only.

Mean daily MMF dose was 1285.7 mg, thereafter increased to 1500 mg from the sixth month. The ST dose was 18.3 mg/24 h, being reduced to 11.8 mg/24 h at month 6, and to 10.1 mg/24 h at month 12; for CSA, the dose was 270 mg/24 h, being reduced to 220 and 165 mg/24 h at months 6 and 12, respectively.

At the study beginning, 8 (31%) patients presented with arterial hypertension, 7 (25%) had plasma creatinine > 2 mg/dL, 15 (53.6%) had microhematuria, all had proteinuria, and in 14 (50%) this was > 3.5 g/24 h. At the study beginning, 21 patients received treatment with angiotensin converting enzyme inhibitors and/or angiotensin receptor antagonists, whereas at the end of the study only 7 patients still received these therapies.

Four patients did not complete the 12-month follow-up period: 1 pregnancy, 1 lack of response, 1 adverse event attributable to MMF, and 1 protocol violation.

For statistical analysis, the SPSS 11.0 statistical package for Windows has been used, determining the Mann Whitney U test and the Wilcoxon's test for quantitative variables and the Pearson's Chi-squared test for qualitative variables, and they were considered significant when the p value < 0.05.

RESULTS

The clinical progression and the course of laboratory parameters have been observed, with mean age of 38.1 ± 11.4 (22-63) years, for the 12-month period of MMF therapy. Table I shows the progression of vital signs and blood laboratory parameters at the different follow-up periods.

Table I. Course of vital signs and blood laboratory parameters

	Baseline	3 months	6 months	12 months	
Weight (kg)	62.4 ± 12.4	61.5 ± 11.9	62.3 ± 12.3	65.7 ± 13.6*	p < 0,05
SBP (mmHg)	133.8 ± 20	130.3 ± 21.8*	128 ± 12.5	127.5 ± 11.9	p < 0,05
DBP (mmHg)	80.9 ± 14	81 ± 14.4	77.1 ± 8.8	75.1 ± 10.7	NS
HR	79.4 ± 7.8	80.6 ± 10.4	78.1 ± 10.7	77.1 ± 6.1	NS
Creatinine (mg/dL)	1.4 ± 0.8	1.3 ± 0.7	1.3 ± 0.8	1.4 ± 1	NS
Albumin (g/dL)	3 ± 0.8	3.4 ± 0.8*	3.5 ± 0.6*	3.9 ± 0.5**	p < 0,01
CrCl (mL/min)	70.9 ± 32.9	67.8 ± 22.5	71.2 ± 27.6	72.3 ± 29.6	NS
RBC (10^6/μL)	4.1 ± 0.6	4.1 ± 0.6	4.2 ± 0.6	4.4 ± 0.4*	p < 0,05
Hemoglobin (g/dL)	12.2 ± 2	12.5 ± 2	12.5 ± 1.8	12.9 ± 1.7	NS
Leucocytes (10^3/μL)	6.5 ± 3.3	7.1 ± 3.1	5.8 ± 2.2	6.4 ± 2.8	NS
Proteinuria (g/24 h)	4.2 ± 2.6	3.1 ± 2.0	2.4 ± 1.7	1.8 ± 2.2*	P < 0,01

SBP = Systolic blood pressure. DBP = Diastolic blood pressure. HR = Heart rate. CrCl = Creatinine clearance. μL = microliter.
*Versus baseline. **Versus baseline p < 0.001.

At the end of the follow-up period, patients had a significant increase of weight, likely due to improved general condition. Five out of 8 hypertensive patients normalized their blood pressure values, only three remaining hypertensive at the end of the study. Systolic blood pressure (SBP) significantly decreased at the third month of therapy, whereas in the remaining periods both SPB and diastolic blood pressure (DBP) remained unchanged. Plasma creatinine and creatinine clearance did not change, while renal function remained stable. No patient required dialysis therapy. Hematological parameters showed a significant increase in red blood cells count, with no severe leukopenia episode and stable leukocytes count. Serum albumin significantly increased from the third month of follow-up and on.

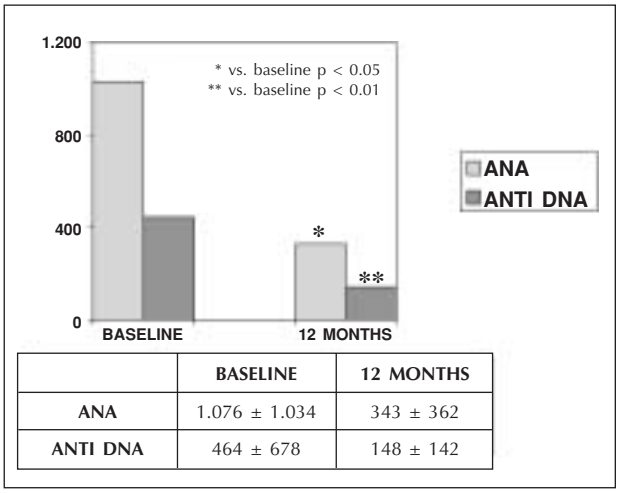
The immunological parameters had a very favorable course; Table II shows the progression of the different complement fractions, highlighting that CH50 significantly increased from the third month of therapy, and the other parameters improved from the sixth month. Figure 1 shows the values of antinuclear antibodies and of anti-DNA antibodies levels. No patient had a lupus relapse during the 12-mopnth follow-up period.

Proteinuria significantly decreased from the third month of treatment (Figure 2). Their values are shown in Table I. When excluding from the proteinuria analysis the five patients treated with CSA, this determination was significant at month 12 of follow-up (3.9 ± 2.1 vs. 2.2 ± 2.4 g/ 24 h, $p < 0.02$). About microhematuria, at the study beginning 53.6% of the patients presented microhematuria, whereas 46.4% did not; at the end of the follow-up period, these values were 20.8% did and 79.2% did not.

According to nephropathy remission criteria used by other authors,[18] 6 (22%) of our patients achieved complete remission, 18 (67%) partial remission, and 3 (11%) had treatment failure. In this analysis, one patient withdrawing from the study because of pregnancy at month 3, was not included.

The drug was well tolerated; four patients had treatment-related adverse effects, in three they were mild not leading to MMF discontinuation. Only one patient discontinued the therapy because of persistent increased of gamma-glutamyl transpeptidase.

In the group of 21 patients being treated with ST plus MMF, the prednisone dose could significantly



	BASELINE	12 MONTHS
ANA	1.076 ± 1.034	343 ± 362
ANTI DNA	464 ± 678	148 ± 142

Fig. 1.—Course of ANA and Anti-DNA.

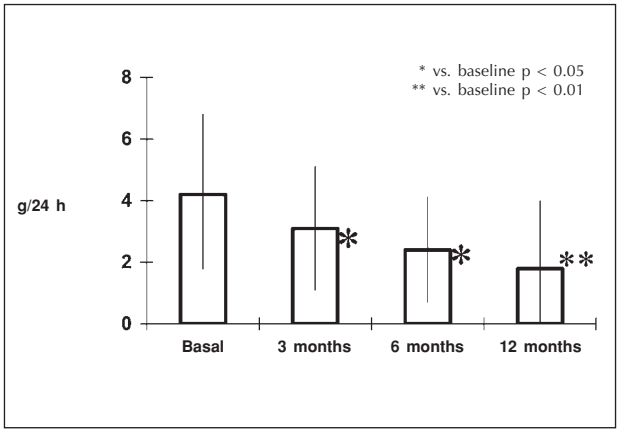


Fig. 2.—Course of proteinuria.

Table II. Course of complement fractions

	Baseline	3 months	6 months	12 months	
C3 (mg/dL)	69.8 ± 26	72.2 ± 19	81.7 ± 23.2*	81.8 ± 18.6*	$p < 0.05$
C4 (mg/dL)	13.7 ± 6.3	15 ± 4	17.4 ± 5.8*	15.7 ± 5.1**	$p < 0.01$
CH50 (mg/dL)	28.1 ± 9.3	55.0 ± 44*	55.5 ± 39.9*	60.9 ± 38.2*	$p < 0.05$

*Versus baseline. **Versus baseline $p < 0,05$.

be reduced throughout the 12-month treatment period (18.3 ± 10.5 vs. 10.1 ± 4.1 mg/day) ($p < 0.01$).

DISCUSSION

The aim of this study was to look for a valid therapeutic alternative for LN, based on what had been published to date. In this sense, we performed an observational prospective study analyzing the course in a group of 28 patients having LN that had not responded to ST and CP therapy, according to clinical and laboratory criteria, and that received MMF associated to ST or CSA.

Although the literature references supporting this MMF-based therapeutic regimen are increasing day by day, most of the works, including ours, had been done in a non-controlled way.

Dooley *et al*. were probably the ones reporting in 1999 the first series of 12 patients suffering from LN that had not responded to cyclophosphamide therapy and were treated with MMF and prednisone (PRD).[5] They observed a decreased in proteinuria and an improvement in immunological parameters, with stable plasma creatinine in all patients. One patient was excluded from the study because of adverse events.

Kingdon *et al*. treated 13 patients with a mean MMF dose of 1000 mg/24 h observing an improvement in anti-DNA levels in 31% of the patients and an increase in complement fractions in 69% of them. The renal biopsy in 11 patients showed mixed lesions of membranous glomerulonephritis and diffuse proliferative glomerulonephritis, and 2 had membranous LN. Creatinine levels significantly improved and proteinuria decreased from 1.5 to 0.9 g/24 h. The patients could discontinue or decrease their steroid dose.[19]

More recently, Kapitsnou *et al*.[20] reported a series of 18 patients suffering from LN, 10 of them achieving complete remission after MMF therapy (complete remission was defined as proteinuria < 0.5 g/day, and normal urine sediment and serum creatinine), 4 partial remission, and 4 having a pathology with type V LN did not respond to the therapy.

Other authors have reported a good course of membranous LN treated with MMF. Thus, Ferro *et al*.[21] reported the clinical course of 10 patients having type V LN, in which proteinuria significantly decreased after one year therapy. Recently, Karim *et al*. have communicated their experience treating class V LN with MMF. They have treated 10 patients observing a decrease in proteinuria and an increase in serum albumin, with no change in plasma creatinine.[22]

Closer in our environment is the experience of Alvarez *et al*.[18], who reported a series of 6 LN patients that after having responded to IVCP and oral ST, presented clinical relapse and were treated with MMF. Three of them achieved complete remission and the three others partial remission, with very few side effects. Karim *et al*.[23] reported a similar experience of lack of response of SLE to treatment with other immunosuppressive agents in a serried of 21 patients that after being treated with MMF their lupus activity, as measured by SLEDAI, proteinuria and ST dose improved. However, by contrast with our work, these patients did not show any improvement in complement fractions or anti-DNA antibodies.

Recently Pisoni *et al*.[24] have published their experience in 86 SLE patients treated with MMF, 59 of whom presented LN with no response to other immunosuppressants; they observed that proteinuria and ST doses were significantly reduced with no changes in plasma creatinine levels or creatinine clearance.

Among controlled studies, we may point out the Euro-Lupus Nephritis Trial, which is a randomized series comparing the response of 90 SLE patients of whom 46 received high-dose therapy with IVCP and 44 low-dose IVCP followed by azathioprine. The results were similar in both groups.[25]

Contreras *et al*. reported the follow-up outcomes of 59 patients treated with IVCP pulses for 7 months, then randomized into three groups: 1) group 1 continued on CP therapy; 2) group 2 switched to MMF; and 3) group 3 switched to azathioprine. Maintenance therapy with MMF or azathioprine showed to be more effective and safe than CP.[26]

In a multicenter study performed by Ginzler *et al*., 140 patients with LN classes III, IV and V, were randomized to receive MMF or IVCP treatment. The MMF-treated group showed higher number of complete remissions than the IVCP-treated group. The total number of partial and complete remissions was 37 in the MMF group and 21 the IVCP group.[27] The number of mild complications was similar in both groups, but the IVCP group presented severe complications requiring hospitalization. This same author carried out another study in which he analyzed the toxicity and tolerability of MMF vs. IVCP concluding that MMF was better tolerated and showed less side effects than IVCP; only MMF showed higher frequency of diarrhea episodes that in no case made necessary treatment discontinuation.[28]

Recently, Chan *et al.*[29] have presented a randomized study on 64 patients, all of them on oral prednisone, and in 33 MMF treatment was associated and 31 received IVCP followed by azathioprine. They concluded that MMF constitutes a good therapy for diffuse proliferative glomerulonephritis of LN, for both the induction and maintenance phases.

The results observed in the 28 patients of our study are similar to those referred in non-controlled studies previously mentioned. We have not observed negative changes in clinical or hematological parameters; creatinine levels and creatinine clearance have remained stable and serum albumin significantly increased. Proteinuria showed a significant decrease at the end of the follow-up period and the percentages of partial remission, complete remission and treatment failure are comparable to those of other authors. On the other hand, complement fractions and ANA and anti-DNA levels have shown, similarly to other works, a significant increase.[18,19,24] Another aspect to be highlighted is that, similarly to other series, steroid doses have decreased and the therapy has been well tolerated.[5,18,19,24]

To conclude, MMF, either associated to steroids or to CSA, may an alternative in LN therapy, acting preserving renal function and achieving a high remission rate with good patient's tolerability and allowing for steroid dose reduction. There are still many issues to be answered regarding the therapy of LN and SLE with MMF, and probably one of the most important ones may be treatment duration.

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