Mycophenolate Mofetil in Lupus Nephritis Refractary to Intravenous Cyclophosphamide

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Objective: To evaluate the use of mycophenolate mofetil (MMF) in lupus nephritis (LN) patients with prior failure to intravenous cyclophosphamide over a 12-month follow-up.
Patients and methods: Eleven patients with LN were included. MMF doses ranged from 1.5-2 g per day. In all patients, 24-h urinary protein excretion, creatinine clearance, and serum creatinine were evaluated. Treatment-related adverse effects were recorded over the 12-month follow-up.
Results: Basal proteinuria decreased from 1.63 g/L (95% CI, 0.78-2.5) to 0.93 (95% CI, 0.1-1.62) g/L at the end of the follow-up period (*P*=.04). Creatinine clearance showed a tendency to improve but no statistically significant differences were found, 69.2 (95% CI, 51.4-87.4) versus 79.29 (95 CI, 49.2-109.3) mL/min, respectively; (*P*=.90). No significant differences were found in the remaining variables. Patients without response to MMF had a higher chronicity index than those with good or average response.
Conclusion: MMF doses of 1.5-2 g per day are a good alternative in LN patients without response to intravenous cyclophosphamide and a low chronicity index. No severe adverse effects were found.

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

Micofenolato de mofetilo en nefritis lúpica refractaria a ciclofosfamida intravenosa

Objetivo: Evaluar el uso del micofenolato de mofetilo (MMF) en pacientes con nefropatía lúpica (NL) y fracaso al tratamiento inicial con ciclofosfamida intravenosa (i.v.), durante un período de 12 meses.
Pacientes y métodos: Se incluyeron 11 pacientes con NL. La dosis de MMF fue de 1,5-2 g/día. Se midieron la depuración de creatinina, creatinina sérica y proteinuria en orina de 24 h; asimismo, se anotaron los episodios adversos con el tratamiento durante los 12 meses.
Resultados: La proteinuria basal disminuyó con MMF de 1,63 (intervalo de confianza [IC] del 95%, 0,78-2,5) a 0,93 g/l (IC del 95%, 0,1-1,62) en el duodécimo mes, con un valor de p = 0,04. La depuración de creatinina tuvo una tendencia a la mejoría; sin embargo, no hubo diferencia estadística, 69,2 (IC del 95%, 51,4-87,4) frente a 79,29 ml/min (IC del 95%, 49,2-109,3), con una p = 0,90. Las demás variables no mostraron diferencias significativas. Los pacientes que no respondieron a MMF tuvieron los índices de cronicidad más altos que los pacientes con respuesta buena o regular.
Conclusión: El MMF a dosis de 1,5-2,0 g/día es una buena alternativa en la NL con bajos índices de cronicidad y con fallo a la ciclofosfamida i.v., sin efectos colaterales graves.

Palabras clave: Nefritis lúpica. Micofenolato mofetilo. Ciclofosfamida. Lupus eritematoso generalizado.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease dependent on B cells, characterized by the production of multiple auto anti-bodies specific to nuclear antigens such as DNA and histones. SLE affects predominantly young women.[1,2] Lupus nephritis (LN) is the most common clinical manifestation of SLE,[3,4] prevalence varies between 35 and 70% in patients with SLE, and these patients have a greater risk of developing kidney failure.[5,6] The presence of immune complexes within the glomerulus has been one of the key elements to develop the inflammatory process seen in lupus nephritis, with the resulting production of in situ inflammatory mediators such as interleukin 6

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Manuscript received October 10, 2005; accepted for publication June 28, 2006.

(IL-6), tumor necrosis factor alpha (TNF), and apoptosis molecules such as FAS-L; a chronic inflammatory episode leads to the formation of what is called the half moon lesions and the characteristic alterations of tubular and interstitial hyalinization seen in this disease.[7,8] Controlled studies from the National Institutes of Health in the United States showed that therapy with intravenous (i.v.) cyclophosphamide was the most effective for proliferative LN, but the infectious episodes and the presence of gonadal insufficiency at early ages have been some of the complications seen with this treatment.[9,10] During the past 4 years, mycophenolate mofetil (MMF) has emerged as an alternative for the treatment of LN. MMF is a pro-drug and its active metabolite is micophenolic acid (MPA), a potent inhibitor of the enzyme inosine 5-monophosphate dehydrogenase (IMPDH), which interferes with T and B cell proliferation. After its oral administration, absorption and conversion of the prodrug in the first half hour is approximately 50% and the peak concentration is achieved around 1 hour after its ingestion. Binding of the drug to serum proteins diminishes when the patient has kidney failure, low serum proteins, or hyperbillirubinemia.[11] AMP suppresses the production of inflammatory cytokines, nitric oxide, and lactic dehydrogenase (LDH) in macrophages.[12,13] Contreras et al[14] showed the therapy with a maintenance dose between 1-3 g/day of MMF after treatment with i.v. cyclophosphamide was better than treatment with i.v. cyclophosphamide every 4 months. Other studies have shown that therapy with MMF as initial treatment improves LN, with a diminished proteinuria and improvement in the physiologic variables of patients with LN.[15]

In this context, our objective was to evaluate patients with LN and failure to initial treatment with i.v. cyclophosphamide, treatment with MMF for a follow-up period of 12 months.

Patients and Methods

Open experimental study, in which 11 patients with a diagnosis of SLE, according to the American College of rheumatology (ACR)[16] and secondary LN defined as persistent proteinuria >0.5 g/L, in 24 hour urine sample, and the presence of hyaline cilindruria in the urinary sediment, were included. Patients included had a failure to previous use of i.v. cyclophosphamide; a failure in treatment was defined as the lack of a reduction in proteinuria in at least 50% of initial values; an increase in serum creatinine of 0.4 mg/dL, in relation to the baseline, an increase in systolic (SP) or diastolic (DP) arterial pressure (AP) of 10 mm Hg with relation to the baseline. In 10 patients a renal biopsy was done. For this study, a "good response" to treatment was defined as a reduction in proteinuria to less than 0.5 g/L in a 24-hour urine sample, "regular" if there was less than a 50% reduction in proteinuria, and "bad" if there was no improvement in proteinuria or if this increased. Patients included in the study did not have evidence of any evident infectious process and women included in the study were not pregnant. For those of MMF administered was 1.5 to 2 g/day, for 12 months; the dose was factioned in 2 administrations, one in the morning and one at night; additionally, patients continued with their customary maintenance dose of prednisone 10 to 20 mg/day. AP was evaluated every 3 months using a mercury sphingomanometer. The complete blood count, serum creatinine, 24 hour creatinine clearance, 24 hour albumin clearance, and serum albumin were evaluated every 3 months. Complement fractions were quantified every 3 months. Biochemical variables were measured automatically with a Vitros 950 system (Ortho-Clinical Diagnostic, Johnson & Johnson Co.). Complement fractions were measured using a Beckman Brea CA nephelometer. A study was approved by the local ethics committee of the Unidad Medica de Alta Especialidad Bajío, IMSS, León, Guanajuato, and patients signed informed consent, according to local law statutes, and to the principles of the Helsinki declaration.

Statistical Analysis

Descriptive statistics were done for demographic and kidney physiology variables; to evaluate the differences between the baseline values and values of 6 and 12 months for proteinuria, a Kruscall-Wallis test was done, and for values of creatinine clearance and serum creatinine ANOVA testing was used.

Results

Mean age of patients included in the study was 25.3±8.85 years; general characteristics of the patients are shown in Table 1. Of the 11 studied patients, 6 had a good response to drug treatment, 3 regular, and 2 bad (2 progress in >6 years to LN). Of the 10 patients biopsied, 6 showed a diffuse proliferative glomerulonephritis (tipe IV) according to the criteria of the World Health Organization (WHO), and in 4 a focal proliferative glomerulonephritis (type III) of the patients with a bad response to treatment, 1 did not undergo kidney biopsy and in the other 2 elevated chronicity indexes were found, in contrast with the ones that had a good and regular response. The relationship to the indexes of activity and chronicity in the response to proteinuria are shown in Table 2. Collateral effects were presented into patients, which forced a reduction in the dosage of the

TABLE 1. Clinical and Demographic Characteristics of Patients With Lupus Nephritis and the Use of Micophenolate Mofetil (MMF) at the Beginning of Treatment*

Age, y	25.3±8.85
Weight, kg	60±17.5
Height, cm	152.7±7.75
BMI, kg/m²	26.1 (22.6-29.6)
PDN, mg/day	14.3±7.76
MMF, mg/day	1593.75 (1393.9-1793.6)
SAP, mm Hg	113.3±12.3
DAP, mm Hg	73.3±9
Creatinine, mg/dL	0.91±0.35
Creatinine clearance,† mL/min	69.2±36.3

*BMI indicates body mass index; DAP, dyastolic arterial pressure; SAP, systolic arterial pressure.
†24 hour urine creatinine clearance.
Values are expressed as medians and standard deviations or means and 95% confidence intervals, according to the case.

TABLE 2. Values of the Activity and Chronicity Indexes in the Kidney Biopsy, Type of Glomerulopathy, and Urinary Protein in Patients With Micophenolate Mofetil Treatment

Patient	Age	Nephropathy Index	Activity Index	Chronicity Index	Baseline Protein	Final Protein
1	23	Type IV	5	2	5.4	0.3
2	28	N/R	N/R	N/R	0.5	0.8
3	19	Type IV	4	5	1.8	1.6
4	31	Type IV	9	1	1.4	0.0
5	36	Type III	3	2	1.1	0.3
6	21	Type IV	3	2	4	2.3
7	26	Type III	3	1	0.8	0.0
8	12	Type IV	17	8	3.1	3.8
9	35	Type III	5	1	0.5	0.0
10	16	Type III	2	3	1.4	0.0
11	39	Type IV	4	1	0.5	0.9

TABLE 3. Values at 0, 6, and 12 Months in Relation to the 24 Hour Urinary Protein Values, kidney Physiology Variables, and Arterial Pressure in Patients With Lupus Nephritis and Micophenolate Mofetil*

	0	6	12	*P*
Urinary protein, g/L	1.63 (0.78-2.49)	1.46 (0.51-2.4)	0.6 (0.1-1.55)	.04
Creatinine clearance†, mL/min	69.2±36.3	73.9±35.9	79.29±44.7	.90
Serum creatinine, mg/dL	0.91±0.35	0.97±0,38	0.91±0.38	.99
SAP, mm Hg	113.33±12.3	118±21.11	114.16±21.51	.35
DAP. mm Hg	73.33±9	74.93±11.92	77.33±14.70	.39
Serum albumin	3.4 (3.1-3.7)	3.2 (2.8-3.6)	3.5 (3-3.9)	.52

*DAP indicates dyastolic arterial pressure; SAP, systolic arterial pressure.
†24 hour creatinine clearance.
The values for 24 hour urinary protein and serum albumin are expressed as medians and 95% confidence intervals; for creatinine clearance, DAP, and SAP, values are expressed as means and standard deviations.

drug: in one of them due to a white cell count of <3000/mL, and in the one due to an upper respiratory tract infection; open episodes improved when dosage was reduced from 2 to 1 g/day, and the rest of the patients had adequate tolerance to the drug. When evaluating the group of patients in treatment with MMF and the reduction in 24 hour urine protein, from the baseline value of 1.63 (0.78-2.49) to 0.6 (0.1-1.55) after 12 months of treatment, was observed with the statistical significance *P*=.04. Values of DAP and SAP, serum albumin, and 24-hour urine protein during the period of study did not show a statistically significant variations (Table 3). Values of C3 serum complement, both at baseline and at month 12 did not show any modifications: 99.2±38.4 versus 90.9±22.2, respectively.

Discussion

The use of i.v. cyclophosphamide is the mainstay of treatment for LN, with high clinical recovery rates, but there are patients that present failure to this therapeutic strategy, and for which searching for other therapeutic strategies is justifiable. MMS in LN as shown in clinical benefit in the majority of the studies are all reported, with less collateral effects than habitual therapy with monthly i.v. cyclophosphamide.[17] In our study, there were no severe collateral effects that could put the patient´s life in danger. After a year of follow-up of these patients, we found that 81% of those evaluated had a good or regular response to the use of the drug, with a reduction in urinary protein that was statistically significant at 12 months in 11 patients,

with a tendency to improve creatinine clearance, though this was not statistically significant. Nonetheless, it must be mentioned that, in spite of this clinical and statistical improvement in the urinary protein as a group, only in 6 of 9 patients in the levels go below 0.5 g/L and into patients there was failure to this treatment. In these 2 patients, chronicity indexes were elevated. Even when the drug improved the urinary protein excretion from the total group, only 54% of patients had a good response, and urinary protein reached levels less than 0.5 g, and 27% had a regular response, with a reduction in urinary protein to less than 50% of the initial values. According to this data, some considerations in the use of MMF in LN must be made. We arbitrarily made 3 groups because, in spite of defining good response to therapy as a reduction of 50% of urine protein, it has been shown that the presence of urine protein in a sustained manner produces tubular damage,[18] and a good response could only be defined as a reduction in the urine protein to a range <0.5 g in a 24-hour urine sample. Prolonged evolution of illness (more than 6 years) and the high chronicity index evaluated in the kidney biopsy influenced the bad response in 2 of our patients. Based on this, the information provided by the kidney biopsy regarding activity and chronicity continues to be fundamental in the prognosis of these patients.[19] In the same way, patients with a failure to treatment have more time since onset with LN. Bujais et al[20] have mentioned the importance of taking into account the time since initial affectation in SLE and the time since onset from the first manifestation, because these 2 factors have prognostic implications. The best therapeutic results can be obtained if the drug is used in the early stages as a first therapeutic option. The majority of the studies that have evaluated MMF in LN are open studies,[21,22] and there is a lack of studies with a larger number of patients, double blinded and in early stages of the illness to enhance the value of this drug as a first choice of treatment in LN, also taking into account that the cost of therapy with MMF is more than with a common used monthly i.v. cyclophosphamide. Current evidence suggests the use of MMF in LN with low indexes of chronicity as a good alternative in patients who have failed monthly i.v. cyclophosphamide, without serious collateral effects, usually related to infectious process and leucopenia.

References

1. Carrol MC. The lupus paradox: natural immunity is protective against disease. Kidney Int. 2004;65:1540.
2. Pisetski D. Systemic lupus erythematosus, epidemiology, pathology and pathogenesis. In: Klippel J, editor. Primer on the rheumatic diseases. Atlanta, GA: Arthritis Foundation Ed.; 1997. p. 246-51.
3. Martins L, Rocha G, Rodríguez A, Santos J, Vasconcelos C, Correia J, et al. Lupus nephritis: a retrospective review of 78 cases from a single center. Clin Nephrol. 2002;57:114-9.
4. Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. Am J Kidney Dis. 2000;35:904-14.
5. Cervera R, Khamashta M, Font J, Sebastián G, Gil A, Lavilla P, et al; and the European Working Party on Systemic Lupus Erythematosus. Systemic lupus erythematosus: Clinical and immunologic patterns of disease expression in a cohort of 1000 patients. Medicine. 1993;72:113-24.
6. Abu Shakra M, Urowitz M, Gladman D, Gough J. Mortality studies in systemic lupus erythematosus results from a single center. I. Causes of death. J Rheumatol. 1995;22:1259-64.
7. Herrera-Esparza R, Barbosa O, Villalobos H, Avalos E. Renal expression of IL-6 and TNF alpha genes in lupus nephritis. Lupus. 1998;7:134-8.
8. Badillo-Almaraz I, Daza L, Avalos-Díaz E, Herrera-Esparza R. Glomerular expression of FAS ligand and BAX mRNA in lupus nephritis. Autoimmunity. 2001;34:283-9.
9. Austin HA III, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986;314:614-9.
10. Gourley MF, Austin HA III, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med. 1996;125:549-57.
11. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinetics. 1998;34:429.
12. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47:85.
13. Jonsson CA, Carlsten H. Mycophenolic acid inhibits inosine 5´-monophosphate dehydrogenase and suppresses production of pro-inflammatory cytokines, nitric oxide, and LDH in macrophages. Cell Immunol. 2002; 216:93-101.
14. Contreras G, Pardo V, Leclercq B, Leonz O, Tozman E, O´Nan P, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971-80.
15. Cross J, Dwomoa A, Andrews P, Burns A, Gordon C, Main J, et al. Renal Association Clinical Trials Subcommittee. Mycophenolate mofetil for remission induction in severe lupus nephritis. Nephron Clin Pract. 2005;100:c92-100.
16. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271-7.
17. Ginzler EM, Aranow C. Mycophenolate mofetil in lupus nephritis. Lupus. 2005;14:59-64.
18. Hill G, Delahousse M, Nochy D, Mandet CH, Bariéty J. Proteinuria and tubulointerstitial lesions in lupus nephritis. Kidney Int. 2001;60:1893-903.
19. Grande JP, Balow JE. Renal biopsy in lupus nephritis. Lupus. 1998; 7:611-7.
20. Bujais S, Ordi-Ros J, Paredes J, Mauri M, Matas L, Cortés J, et al. Contribution of the inicial features of systemic lupus erythematosus to the clinical evolution and survival of a cohort of Mediterranean patients. Ann Rheum Dis. 2003;62:859-65.
21. Ding L, Zhao M, Zou W, Liu Y, Wang H. Mycophenolate mofetil combined with prednisone for diffuse proliferative lupus nephritis: a histopathological study. Lupus. 2004;13:113-8.
22. Chan TM, Tse KC, Tang CS, Mok MY, Li FK. Long-term study of mycophenolate mofetil as continous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol. 2005;16:1076-84.