Mycophenolate Mofetil in Lupus Nephritis Refractory 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 = 0.04). 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 = 0.90). 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.
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. 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 hyperbilirubinemia. AMP suppresses the production of inflammatory cytokines, nitric oxide, and lactic dehydrogenase (LDH) in macrophages. Contreas et al 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.

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) 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 0.3 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 fractioned 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 sphygmomanometer. 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 (type 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
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 \(P=0.04\). 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 renal function as a group, only 6 of 9 patients in the levels go below 0.5 g/L and into patients there was failure to this improvement. 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 as a decrease 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. Baijat et al20 have mentioned the importance of taking into account the time since initial affectation in SLE and the time since diagnosis 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