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Mycophenolate in Refractory and Relapsing Lupus Nephritis

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Key Words
Refractory/relapsing lupus nephritis · Systemic lupus erythematous · Mycophenolate

Abstract
Background: Mycophenolate (MF) is effective as induction and maintenance treatment in patients with lupus nephritis (LN). This study evaluates the efficacy and safety of MF in patients with refractory and relapsing LN. ***Methods:*** Data were retrospectively obtained for 85 patients (35 refractory and 50 relapsing) from 11 nephrology departments in Spain. The primary endpoints were the incidence and cumulative number of renal responses and relapses and their relationship with baseline clinical and analytical data. The secondary endpoint was the appearance of side effects. ***Results:*** The main clinical and analytical variables were similar both in refractory and relapsing LN. Most of the patients had received cyclophosphamide, and all of them switched to MF. 74 patients (87%) achieved a response (69% partial, 31% complete). Age at starting MF, gender, pathological classification, body mass index, blood pressure, baseline renal function, and proteinuria were not associated with achieving response. After stopping MF, 3 of 19 patients (15.7%) relapsed, all at 6 months of follow-up. No differences were found between clinical and analytical variables and number of relapses. Side effects were unremarkable, except for 1 patient, who died of thrombocytopenia and ovarian hemorrhage. ***Conclusions:*** Switching to MF from other immunosuppressive treatments is effective and safe in refractory and relapsing LN.

Introduction

The treatment of severe lupus nephritis (LN) using standard immunosuppressive regimens based on cyclophosphamide (CYC) and corticosteroids is affected by failure to respond, multiple relapses, and severe side ef-

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fects such as infertility, infection, and malignancy. Both renal prognosis and vital prognosis are poor. Several reasons have been posited for failure to respond, including ethnicity and underlying disease. Therefore, alternative strategies for the management of refractory or severe relapsing LN are necessary [1, 2].

Mycophenolate (MF) is considered to be efficacious and safe as induction and maintenance treatment in LN, with fewer adverse effects than CYC-based strategies [3, 4]. Furthermore, this favorable profile has been observed in patients with renal impairment [5–7]. Although no randomized clinical trials have been performed in patients with CYC-refractory and relapsing LN, several reports and small cases series have shown that MF is highly effective and well tolerated and that it could be a good alternative in patients with LN [8–10]. Therefore, the role of MF in refractory and relapsing LN and its association with baseline clinical and analytical data is worth investigating.

Using data from our national survey on the use of MF to treat LN, we performed a retrospective, uncontrolled study involving 85 patients from 11 centers in Spain to assess the efficacy and safety profile of MF in patients with refractory or relapsing LN and its association with clinical and analytical data.

Subjects and Methods

Patients

Based on a uniform protocol, 11 nephrology departments belonging to the Spanish Group for the Study of Glomerular Disease (GLOSEN) collected data from patients with LN who had received MF. We previously reported on the role of MF as induction therapy [5] and maintenance therapy [6] in LN. The inclusion criteria in the current investigation were as follows: (i) diagnosis of systemic lupus erythematous according to the criteria of the American College of Rheumatology, (ii) biopsy-proven LN, (iii) use of MF in refractory or relapsing LN, and (iv) treatment for a minimum of 3 months. The criteria for refractory and relapsing LN were based on personal expertise or established local treatment regimens and consisted mainly of failure to achieve renal remission after at least 6 months of intensive treatment with immunosuppressive drugs or more than 2 relapses after having achieved renal remission. The exclusion criteria were any conditions in which MF was contraindicated. No comparisons were made with other immunosuppressive maintenance therapies.

Data Collection

Data were compiled from the medical records of the participating centers and included age, gender, ethnicity, histopathological class (at diagnosis of LN) according to the 2003 classification of the International Society of Nephrology/Renal Pathology Society, previous medication (type and dose), body mass index (kg/m^2), and blood pressure (mm Hg). Analytical variables included hemoglobin (g/dl), white cell counts ($cells/mm^3$), serum creatinine (mg/dl), estimated glomerular filtration rate (eGFR, $ml/min/1.73\ m^2$) calculated using the 4-variable Modification of Diet in Renal Disease equation (eGFR = 175 × serum creatinine – 1.154 × age – 0.203 × 1.210 [if black] × 0.742 [if female]), proteinuria (g/24 h), titers of antinuclear and anti-dsDNA antibody, and levels of complement fraction (C_3 and C_4, mg/dl). Types and doses of MF (mofetil or enteric-coated MF sodium), corticosteroids, and antihypertensive drugs were also recorded. We also recorded complications occurring during treatment, side effects, occurrence of end-stage renal disease (need for chronic dialysis or renal transplantation), and deaths. Data were recorded when starting MF (baseline) and at 3, 6, and 12 months and then every 6 months up to 60 months. Outcome after discontinuation of MF was evaluated.

Responses (partial or complete) and relapses were defined according to the criteria of our previous studies [5, 6]. Complete response was defined as a return to normal or previous eGFR and proteinuria ≤0.5 g/24 h. Partial response was defined as a decrease in proteinuria to <3.5 g/24 h and a ≥50% decrease in proteinuria in patients with baseline proteinuria ≥3.5 g/24 h, or as a 50% decrease in proteinuria in patients with baseline proteinuria <3.5 g/24 h. In both situations, eGFR had to have stabilized (±25%) or improved. Relapse after MF treatment was defined as doubling of proteinuria (≥1 g/24 h in patients with ≤0.5 g/24 h at initiation of MF treatment, and ≥2 g/24 h in patients with >0.5 g/24 h at initiation of MF treatment) or as a ≥50% decrease in eGFR. The response rate and number of relapses were evaluated at each assessment point during follow-up.

Endpoints

The primary endpoints of the study were as follows: (i) incidence and cumulative number and percentage of patients who achieved a renal response (complete or partial) while receiving MF, (ii) incidence and cumulative number and percentage of patients who experienced a renal relapse after stopping MF, and (iii) relationship between response rates or number of relapses and clinical and analytical data at baseline. The secondary endpoints were the appearance of side effects, number of cases that progressed to end-stage renal disease (need for chronic dialysis or renal transplantation), and deaths.

Statistical Analysis

Continuous variables were reported as mean ± SD or median (range), according to their Gaussian distribution. Qualitative variables were reported as percentages. Continuous data were compared using an unpaired t test or Mann-Whitney test, as appropriate. The chi-square and Fisher exact tests were used to compare qualitative variables. Serial data were compared using repeated-measures analysis (paired t test or Wilcoxon test). The incidence and cumulative number and percentage of responses and relapses were estimated using Kaplan-Meier plots and analyzed using the log-rank test. We calculated the hazard ratio (HR) and 95% CI using the univariate Cox proportional hazards model. Logistic regression (Cox proportional hazards) was applied to explore the relationships between variables. Statistical significance was set at $p < 0.05$ (2-tailed). The statistical analysis was performed using SPSS Statistics Version 20.

Table 1. Baseline characteristics at initiation of MF in refractory and relapsing LN

	Refractory (n = 35)	Relapsing (n = 50)	p[a]
Age, years (mean ± SD) at:			
Diagnosis of systemic lupus erythematosus	24±12	26±9	0.37
Renal biopsy	29±12	32±13	0.23
Initiation of MF	30±11	37±18	0.01
Gender (F/M ratio)	4	4	1
Previous treatments, n			
Cyclophosphamide	28	45	0.32
Azathioprine	11	20	0.56
Cyclosporine A	3	6	0.88
LN class at the beginning of induction therapy, n			
II	0	1	
III	15	14	0.35
IV	16	31	
V	4	4	
Body mass index (mean ± SD)	25.4±4.8	26.7±5.8	0.37
Mean blood pressure, mm Hg (mean ± SD)[b]	90.6±14.2	97±16.5	0.10
Hemoglobin, g/dl (mean ± SD)	13±1.5	12.5±1.6	0.18
Leukocytes, mm^3 (median)	7,141±3,147	6,296±2,688	0.19
Serum creatinine, mg/dl (mean ± SD)	1.1±0.5	1.1±0.6	
Median, mg/dl	1	1	0.95
Range	0.5–2.6	0.4–3.7	
eGFR, ml/min/1.73 m^2, MDRD-4 (mean ± SD)	73.1±33.8	72±42.6	0.9
Proteinuria, g/24 h (mean ± SD)	3.9±3.4	2.7±2.4	
Median, g/24 h	3.1	2.5	0.06
Range	0.07–12.4	0.01–10.9	
ANA, 1/titer (median)	320	320	0.79
Anti-DNA, 1/titer (median)	30	4	0.09
C3, mg/dl (mean ± SD)	77.6±25.4	71.5±26.8	0.30
C4, mg/dl (mean ± SD)	14.3±9.3	12.1±8.8	0.30
MF type, n[c]			
Mofetil	27	44	
Enteric-coated sodium	8	6	0.36
MF dose, mg/dl (mean ± SD)	1,292±455	1,060±483	0.02
Median, mg/24 h	1,000	1,000	
Range	500–2,000	250–2,000	
Prednisone dose, mg/dl (mean ± SD)	20±10	30±15	
Median, mg/24 h	20	27	0.05
Range	5–40	5–60	
Follow-up, months (mean ± SD)	39.2±27.8	38.5±25.6	
Median, months	30	30	0.85
Range	6–102	3–102	

MDRD = Modification of Diet in Renal Disease; C = complement. [a] Refractory patients vs. relapsing patients. χ^2 test, t test, or Mann-Whitney test, as appropriate. [b] Diastolic pressure – (differential blood pressure)/3. [c] 250 mg of MF mofetil = 180 mg of MF sodium.

Results

The study sample comprised 85 patients (35 with refractory disease and 50 with relapsing disease) who met the inclusion criteria. The main clinical and analytical variables were similar in both forms, except for age at starting MF, which was higher in relapsing forms than in refractory forms (37 ± 18 vs. 30 ± 11 years, p = 0.01), and initial dose of MF, which was slightly higher in refractory forms (table 1).

Table 2. Clinical data and laboratory values at baseline and after treatment in refractory and relapsing LN

	Baseline	3rd month	6th month	12th month	24th month	36th month	48th month	60th month
Mean blood pressure, mm Hg[a]	94±15	92±12	87±12*	88±10*	89±11	87±10	87±10	88±8
Hemoglobin, g/dl[a]	12.7±1.6	13.0±1.4	12.8±1.5	12.8±1.3	12.6±1.4	13.0±1.4	13±1.3	12.7±1.7
Leukocytes, mm^{3}[a]	6,651±2,901	6,832±2,728	6,306±2,552	6,210±2,305	6,366±2,603	6,103±1,974	6,535±2,483	5,984±2,844
Serum creatinine, mg/dl[b]	1.0	1.0	0.9	0.9	0.9	0.9	0.8	0.8
eGFR, ml/min/1.73 m^2, MDRD-4[a]	72±39	72±28	77±39	74±39	75±41	80±43	86±27	86±42
Proteinuria, g/24 h[b]	2.8	1.0*	0.9*	0.5*	0.3*	0.3*	0.3*	0.5*
ANA, 1/titer[b]	320	160*	160*	250*	160*	160*	160*	160
Anti-DNA, 1/titer[b]	10*	2*	2*	2*	2*	2*	2*	2*
C_3, mg/dl[a]	74±25	87±25*	88±23*	89±27*	91±23*	85±23*	90±28*	82±21
C_4, mg/dl[a]	13±9	16±9*	16±10*	18±10*	15±8*	15±7*	15±6*	13±7
Mycophenolate dose, g/24 h[b]	1,000	1,500*	1,500*	1,500*	1,250*	1,000	1,000	1,000
Prednisone dose, mg/24 h[b]	20	15*	10*	7.5*	5*	5*	5*	5*

[a] Mean ± SD. [b] Median. * Versus baseline values, $p < 0.05$ (paired t test or Wilcoxon test, as appropriate). MDRD = Modification of Diet in Renal Disease; ANA = antinuclear antibodies.

All the patients were Caucasian and Spanish. Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. With regard to previous treatments, most patients (73, 85.8%) had received CYC (28 in refractory forms and 45 in relapsing forms); the median number of pulses was 7 and the median dose of CYC pulses was 0.83 g (range, 0.5–1.8). Thirty-one patients (36.4%) had received azathioprine at a median dose of 1.5 mg/kg/day for 18 months (11 in refractory forms and 20 in relapsing forms), 9 patients (10.5%) had received cyclosporine A at a median dose of 2 mg/kg/day for 12 months (3 in refractory forms and 6 in relapsing forms), and 3 (3.5%) had received intravenous immunoglobulin (all in relapsing forms). These treatments were frequently used as sequential therapy in the same patient. All the patients were also treated with corticosteroids at different doses, although the cumulative dose of each drug was similar in both forms.

At initiation of treatment with MF, 53 patients (62.3%) had normal renal function (eGFR ≥60 ml/min/1.73 m^2) and 32 (37.6%) had impaired renal function (eGFR <60 ml/min/1.73 m^2); only 9 patients (10.6%) had eGFR <30 ml/min. All of the patients received renin-angiotensin blockers. The median follow-up was similar in both forms (30 months). During treatment with MF, 10 patients received tacrolimus (4 in relapsing forms and 6 in refractory forms), and 2 patients received cyclosporine (1 in each form).

Paired tests showed that values for hemoglobin, leukocyte count, serum creatinine, and eGFR during treatment did not differ from baseline values. Renal function did not change during follow-up in patients with normal renal function, whereas in patients with baseline renal failure, eGFR increased from 40 ± 13 ml/min/1.73 m^2 to 48 ± 19 ml/min/1.73 m^2 at 6 months (paired t test, $p < 0.001$), 49 ± 22 ml/min/1.73 m^2 at 12 months (paired t test, $p < 0.001$), and 52 ± 21 ml/min/1.73 m^2 at 24 months (paired t test, $p < 0.001$). Levels of C_3 and C_4 and dose of MF increased significantly, while mean blood pressure, titers of antinuclear and anti-dsDNA antibody, proteinuria, and dose of prednisone decreased significantly (table 2).

Primary Endpoints

Renal Relapse and Response

During follow-up, 74 patients (87.1%) had a response. Fifty-one achieved a partial response (69%), and the remaining 23 patients (31%) achieved a complete response. The incidence and cumulative number of responses during treatment with MF are detailed in figure 1. Partial responses were more frequent than partial responses at each period of follow-up (fig. 2). The median time to response was 3 months. The univariate and multivariate analyses showed that age at starting MF, gender, LN class (class III and IV or class II and V), body mass index, blood pressure, eGFR (presence or absence of renal failure), and proteinuria were not independent variables for achieving response ($p > 0.05$).

We recorded data on the progress of 19 patients (22.3%) after discontinuation of MF (follow-up, 14.5 ± 11.7 months; median 12 months, range 6–48 months). Three patients (15.7%) relapsed at 6 months. The treatment im-

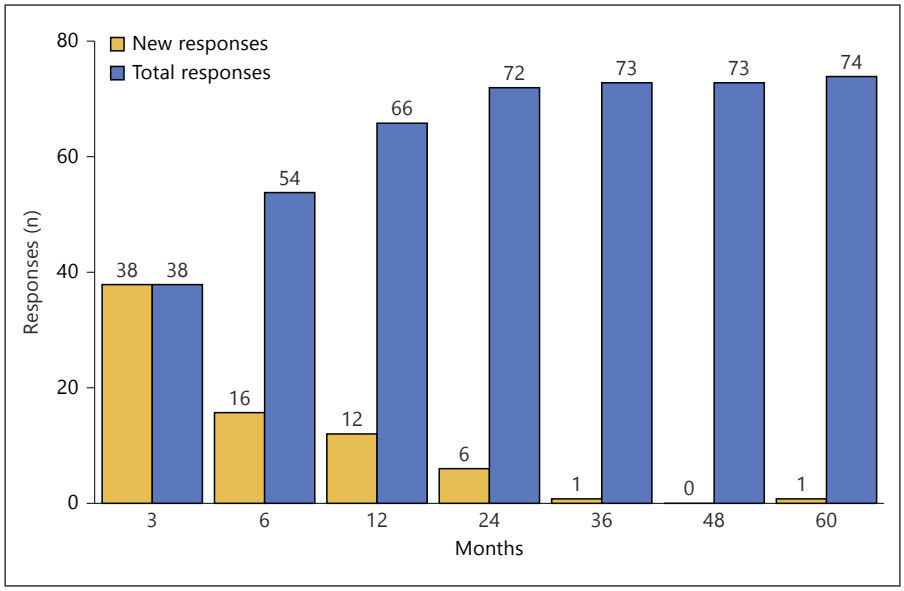

Fig. 1. Monthly incidence and cumulative number of responses during treatment with MF.

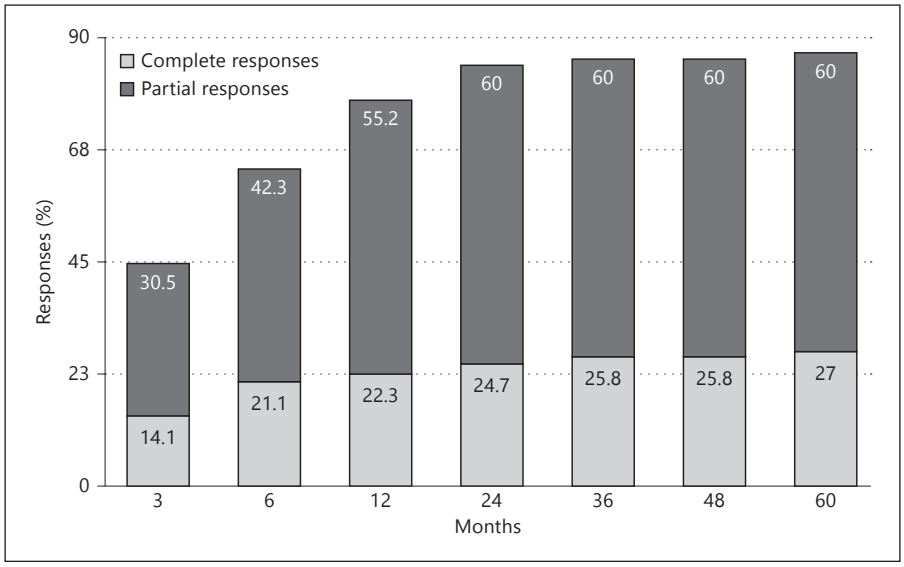

Fig. 2. Percentage of complete and partial responses after the onset of MF treatment.

mediately prior to relapse was low-dose prednisone (10 mg/day) in all 19 patients and concomitant AZA (50 mg/day) in 1. Two relapsing patients had renal failure (eGFR <60 ml/min), and 1 had normal renal function ($p = 0.051$). No differences were found between the number of relapses and clinical and analytical variables ($p > 0.05$).

Secondary Endpoints

With regard to adverse effects, 20 patients (23.5%) presented infections (7 of unknown origin, 3 uncomplicated urinary tract infections, 3 candidiasis, 3 herpes zoster, 1 pneumonia, 1 *Pneumocystis jiroveci* infection, 1 listeriosis, and 1 cytomegalovirus), 13 patients (15.3%) developed gastrointestinal symptoms (nonspecific discomfort and diarrhea), 2 cutaneous rashes, 1 thrombocytopenia, and 1 amenorrhea (table 3). Five patients (5.8%) developed end-stage renal disease, and 1 died as a result of thrombocytopenia and massive ovarian hemorrhage (probably related to the treatment). Treatment with MF had to be withdrawn in 32 cases (37.6%), mainly at the physician's request (22 cases), although in 10 cases treatment was withdrawn at the patient's request.

Table 3. Adverse effects and outcome (n) in refractory and relapsing LN treated with MF

Effects/outcome	Total
Side effects	
Gastrointestinal	13
Infections	20
End-stage renal disease	5
Deaths	1

Discussion

We investigated the efficacy and safety profile of MF in patients with refractory or relapsing LN previously treated with other immunosuppressive drugs and the association between baseline variables and treatment with MF. Our results add data to those obtained in a Spanish national survey about the role of MF as induction and maintenance treatment in LN [5, 6]. The current study has the following characteristics. First, we analyzed refractory and relapsing forms of LN together, as this is the approach generally adopted in the literature [8, 11–14]. Second, as histological classification was not a criterion for inclusion but response to treatment was, we did not exclude the patient with Class II LN because histological transition could have occurred. Third, we selected patients according to the criteria of each participating nephrology department, since no consensus had been reached on whether LN should be considered refractory or relapsing when we performed our investigation. Indeed, detailed criteria for defining LN as refractory or relapsing are missing from most studies, except 2 [9, 15], in which failure to respond was based on the persistence of severe renal damage after at least 2 intensive courses of standard immunosuppressive treatment. Therefore, a definition of refractory disease has been proposed and can be applied in future studies [16]. Finally, hematuria and red cell casts are not considered to be criteria for response in LN for several reasons, as recently reported by Bose et al. [17]. Nevertheless, and although our investigation is neither controlled nor prospective, our findings do provide valuable data on the role of MF in uncontrolled LN in a representative Spanish population.

High-quality clinical trials investigating induction and maintenance treatment of LN have been performed [3, 4], although powerful studies on refractory or relapsing LN in which standard treatments based on CYC and corticosteroids had failed are lacking. Given that an extended course of CYC is remarkably inferior to initial administration and that the cumulative dose could be associated with severe adverse effects, other immunosuppressive agents have been used. Of these, MF is the most widely tested and could therefore be a good alternative, as we report here. All patients from the current study switched from other immunosuppressive treatments, mostly CYC and AZA, to MF after being unable to achieve a response and/or relapsing.

The first clinical series of patients with relapsing or refractory LN after treatment with CYC who received MF were published in the late 1990s and revealed an improvement in proteinuria and renal function [8, 18–20]. Subsequently, several observational and uncontrolled studies also described the beneficial effect of MF in refractory or relapsing LN, indicating that switching from CYC to MF is a reasonable alternative strategy [9–14, 21–29]. Since the dose of prednisone in our study was low and decreased during follow-up, administration of MF could obviate the need for corticosteroids [8, 9, 18, 30]. Current clinical practice guidelines recommend switching to an alternative agent in patients who do not achieve a partial response after 6–12 months or who do not reach a complete response after 2 years of treatment [31, 32]. Furthermore, the American College of Rheumatology [33] and KDIGO guidelines also recommend a non-CYC-based regimen when the initial treatment fails in order to avoid excessive exposure to CYC [16]. Although the criteria for switching from CYC to MF in the papers mentioned above are not uniform, the results reported are consistent with ours, which indicated a favorable rate of response (87%) and a low rate of renal relapse (15%). Even though improvement in LN is often delayed after the completion of a previous course of treatment (the *'carry over'* effect), it seems that the role of MF in uncontrolled cases is rarely related to previous treatments. Nevertheless, it could be interesting to determine the relationship between previous treatments and responses after MF. We were not able to obtain reliable data analyzing differences in responses to MF in patients who were initially treated with AZA or CYC. Given our retrospective design, many patients received sequential regimens, most of which start with CYC followed by AZA or other drugs. Therefore, we cannot separate our patients according to previous uniform scheduled treatment. However, this limitation, which is common in retrospective and observational studies, does not invalidate our results, because our aim was to investigate the role of MF in LN patients with inadequate response to standard treatment, irrespective of previous therapy. While ethnicity plays a role in the response to immunosuppressive treatment in LN [34], it seems that

the response to MF in refractory or relapsing disease does not differ in patients from different ethnic groups. In fact, the cases reported to date are from the USA [8, 18, 19], South America [13, 26], Canada (in children) [35], Europe [9, 10, 12, 14, 20, 23–25, 30], Australia [21], and Asia [11, 22, 27–29].

Despite the usefulness of MF in unresponsive LN, response was not achieved in about 13% of cases in our study. Therefore, it is worth considering adding alternative immunosuppressive drugs or investigating other strategies. The efficacy of calcineurin inhibitors has been reported [14, 18, 23], and 14% of our patients were also treated with tacrolimus or cyclosporine. Therefore, the combination of low-dose MF and calcineurin inhibitors seems to be a valuable alternative [15]. However, these results have to be confirmed in well-designed clinical trials.

In some published cases, follow-up renal biopsies have revealed a decrease in the severity of histological lesions in patients with LN [11]. However, this approach was not followed in most reported cases. On the other hand, we found an increase in eGFR in patients treated with MF in the group with an initial decrease in renal function; therefore, we can speculate that histological lesions could improve after treatment with MF.

One of the most intriguing findings concerns the role of MF when renal function is impaired. In most reported series, patients with impaired renal function were excluded. Moreover, when cases with renal insufficiency were included [8, 9, 13], the role of MF was not analyzed. According to our results, the presence of renal failure does not seem to affect the response to MF, since the rates of response and relapse were similar in cases with normal renal function and in those with impaired renal function. Curiously, none of the remaining variables (e.g., age, gender, blood pressure, proteinuria, and histological class) have been found to be indicators of relapse or response.

The dose of MF is associated with its efficacy and, above all, with side effects. Interestingly, the dose of MF administered in most studies is relatively low, hardly ever more than 2 g/day. In fact, Weng et al. [29] found that Oriental patients might respond to lower doses (between 0.5–1 g/day) than Caucasians. According to these authors, this strategy could be extrapolated to other ethnic groups, as we also confirmed in our investigation in which the most frequent dose of MF administered was 1.5 g/day or its equivalent (720 mg bid [enteric-coated form]). Therefore, a dosage in the range of 0.5–1.5 g/day may be sufficient in most patients with refractory or relapsing LN.

The most frequent adverse effects are infections, gastrointestinal intolerance, and leukopenia [8–12]. Although these appear in about 20–30% of cases, most are mild [30]. In general, MF is well tolerated and discontinuation is rarely necessary. In our study, the rates of adverse effects were similar to those described by other authors. The only severe (and probably related) toxicity was that affecting the patient who died of severe thrombocytopenia and massive ovarian hemorrhage. Unfortunately, no reliable data are available on the role of antimalarial drugs and co-trimoxazole in renal outcome or on the onset of complications.

Our study is limited by its retrospective and multicenter nature, as were our previous studies on induction and maintenance treatment in MF [5, 6]. According to our results, MF could be the preferred choice of treatment in relapsing or refractory LN. However, other alternatives as anti-CD20 monoclonal antibodies and other new treatments remain to be clarified because there are not comparative studies on the utility of MF and other schedules of treatment. However, our data provide strong justification for treating LN with MF as an alternative drug when other immunosuppressive treatments, mostly CYC-based regimens, have failed.

We conclude that MF is a suitable alternative in refractory and relapsing LN in which other immunosuppressive schedules have failed.

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Conflict of Interests

The authors of this manuscript declare that they have no conflicts of interest.

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