Longterm Followup After Tapering Mycophenolate Mofetil During Maintenance Treatment for Proliferative Lupus Nephritis

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ABSTRACT. ***Objective.*** To determine the timing for safe reduction of mycophenolate mofetil (MMF) dose during remission-maintenance therapy of proliferative lupus nephritis.

Methods. The study population consisted of 44 patients evaluated retrospectively; MMF dose was empirically tapered in 18/44 patients until the latest observation.

Results. Patients reducing MMF ≤ 18 months after remission/complete remission had a 6.8-fold/6.3-fold higher risk of relapse compared to those taking a stable dose ($p = 0.001$, $p = 0.011$, respectively). Reducing MMF later than 18 months was not associated with increased relapse rates.

Conclusion. Reducing MMF > 1.5 years after remission/complete remission seems to warrant drug tapering without increased risk of disease flare in proliferative lupus nephritis. (J Rheumatol First Release April 15 2011; doi:10.3899/jrheum.101249)

Key Indexing Terms:
LUPUS NEPHRITIS MAINTENANCE TREATMENT MYCOPHENOLATE MOFETIL

The role of mycophenolate mofetil (MMF), an immunosuppressant with inhibitory effects on T and B lymphocytes, in the treatment of proliferative lupus nephritis has been increasingly recognized[1,2,3,4,5]. However, the increased risk of side effects complicating longterm immunosuppression[6], along with the undetermined cost-benefit ratio of long-standing treatment, have generated questions regarding the optimal duration of therapy in patients with quiescent disease.

MATERIALS AND METHODS

Medical records were reviewed for a total of 75 patients, followed at the Department of Pathophysiology, National University of Athens, who received treatment with MMF for biopsy-proven proliferative lupus nephritis[7,8] between 2000 and 2010. Patients with an irregular record or lost to followup (n = 4), those who failed to achieve remission (n = 20), and those with a followup time < 1 year receiving MMF (n = 7) were excluded. Thus, the study group consisted of 44 patients. Treatment regimens, approved by the hospital ethical committee, included either the use of 6 monthly intravenous (IV) pulses of cyclophosphamide (CYC) 1 g/m^2 in association with IV pulses of methylprednisolone 1 g for the induction of remission followed by maintenance treatment with 2 g/day MMF (n = 22)[2], or induction-maintenance treatment with MMF 2 g/day (n = 17) or 3 g/day (n = 5)[3]. All patients received oral methylprednisolone 0.5–1 mg/kg/day for 1 month with subsequent tapering based on the extrarenal disease activity. No patient required additional administration of IV corticosteroid for persistent renal activity.

The MMF dose was tapered in 18 patients based on the physician's clinical assessment (10/22 patients on MMF maintenance treatment after CYC induction; 8/17 receiving 2 g/day MMF given as induction-maintenance treatment — Group 1). All patients were in renal remission and had no signs of extrarenal activity at the time of drug tapering. No patient tapered treatment because of drug toxicity. MMF was initially reduced from 2 g/day to 1.5 g/day in 7 patients within a median time of 22 months after the initial response. A subsequent reduction to 1 g/day was ordered in 4 of these patients within a median time of 7.5 months. Three of the 4 patients reduced the drug further to 0.5 g/day after another median time of 6 months and the fourth discontinued treatment 12 months after the previous dose reduction. Another 11 patients initially reduced MMF to 1 g/day within a median treatment duration of 17 months after the initial response. A further gradual reduction was ordered in one of these patients. MMF was reduced to 0.5 g/day 6 months after the first dose reduction and it was finally discontinued after another 6 months. In the remaining 26 patients, the MMF dose was stable until the end of followup (Group 2).

The occurrence of renal relapse and MMF-related adverse events was recorded.

Definitions. Renal remission was defined as the presence of all the criteria given below in at least 2 measurements 1 month apart: (1) decrease ≥ 50% in proteinuria and proteinuria < 3 g/24 h; (2) absence of hematuria: ≤ 5 red blood cells (RBC) per high power field (hpf); (3) absence of pyuria: ≤ 5 white blood cells (WBC) per hpf; (4) absence of cellular casts (< 1/hpf); and (5) stable glomerular filtration rate (GFR; fluctuations within 10% of the initial value) if baseline serum creatinine < 2 mg/dl or improvement ≥ 30% if baseline serum creatinine ≥ 2.0 mg/dl. Complete renal remission was considered if the patient presented with all the criteria given below in at least 2 measurements 1 month apart: (1) 24 h proteinuria ≤ 500 mg; (2) RBC ≤ 5/hpf; (3) WBC ≤ 5/hpf; (4) absence of cellular casts (< 1/hpf); and (5) GFR ≥ 80 ml/min/1.73[3]. Renal relapse was defined as: (1) increase ≥ 50% in proteinuria and proteinuria > 1 g/24 h; and/or (2) hematuria (RBC > 5/hpf); and/or (3) pyuria (WBC > 5/hpf); and/or (4) cellular casts (≥ 1/hpf); and/or (5) decrease ≥ 30% in GFR in at least 2 measurements.

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Statistical analysis. Patient characteristics were compared using nonparametric statistical tests. Cox regression models were applied to define factors associated with renal relapse and results were expressed as hazard ratios (HR). Time-dependent analysis was performed for MMF dose reduction, MMF dose and complete renal remission in order to account for the differential baseline risk associated with those conditions. Patients reducing MMF were classified into subgroups of different risk according to the time of drug reduction after initial response. Based on the number of events, a period of 18 months was chosen. Kaplan-Meier survival curves for the time from MMF dose reduction to relapse were produced in a subgroup analysis including the 18 subjects of Group 1. The association between MMF-related adverse events and treatment duration was tested using binary logistic regression.

RESULTS

Patients' baseline characteristics did not differ significantly between the 2 groups (Table 1). Although diffuse proliferative as well as mixed proliferative and membranous disease seemed to be underrepresented in Group 1, the distribution of nephritis classes did not differ significantly between the 2 groups. Further, the induction treatment protocols were distributed equally in Groups 1 and 2 (p = 0.540). Although the entire treatment duration was longer in Group 1, the treatment duration with a stable, nonreduced MMF dose was similar between the 2 groups (Table 1).

Renal flares were more frequent in Group 1 (56% vs 23% in Group 2; HR 3.37, p = 0.024; Table 2). Irrespective of group, the risk of renal flare was 44% lower per 0.5-g dose increase of MMF (p = 0.011). In univariate Cox regression, patients who reduced treatment 18 months or earlier after remission or complete remission had a 6.8-fold and 6.3-fold, respectively, higher risk of relapse compared to Group 2

Table 1. Patient and treatment characteristics.

Characteristics	All Patients, N = 44	Group 1, N = 18	Group 2, N = 26	p
Age, median (range), yrs	30 (15–56)	28.5 (15–54)	31.5 (17–56)	0.333
Male:female	6:38	2:16	4:22	1.00
SLE duration, median (range), mo	42 (0–312)	36.5 (1–173)	46 (0–312)	0.990
Nephritis duration, median (range), mo	17.5 (0–218)	19.5 (1–168)	11 (0–218)	0.351
WHO class, II; IV; V with III/IV lesions	24; 11; 9	12; 3; 3	12; 8; 6	0.478
Activity index	4 (2–18)	3.5 (2–8)	4 (2–18)	0.787
Chronicity index	2 (0–8)	1 (0–6)	2 (0–8)	0.307
Anti-dsDNA antibody (%)	44 (100)	18 (100)	26 (100)	1.00
Anti-Ro antibody (%)	2 (48)	7 (30)	14 (54)	0.329
Anti-La antibody (%)	6 (14)	4 (22)	2 (8)	0.208
Anti-U1RNP antibody (%)	8 (18)	2 (11)	6 (23)	0.439
Anti-Sm antibody (%)	5 (11)	2 (11)	3 (12)	1.00
Antiphospholipid antibody (%)	20 (45)	11 (61)	9 (35)	0.103
Low C3 at baseline, < 70 mg/dl (%)	22/34 (65)	7/13 (54)	15/21 (71)	0.462
Low C4 at baseline, < 10 mg/dl (%)	22/34 (65)	8/13 (62)	14/21 (67)	1.00
GFR at baseline, median (range), ml/min/1.73 m^2	82 (21–137)	76 (21–120)	85 (24–137)	0.377
Urine protein levels at baseline, median (range), g/24 h	1.3 (0.1–9)	1.5 (0.2–7)	1.2 (0.1–9)	0.867
≥ 3 g/24h (%)	12/38 (32)	5/16 (31)	7/22 (32)	0.970
Urine protein levels of nephrotic range, ≥ 3 g/24 h	4 (3–9)	3.5 (3.1–7)	4 (3–9)	0.935
< 3 G/24 H (%)	17/38 (45)	8/16 (50)	9/22 (41)	0.578
Urine protein levels of subnephrotic range (≥ 0.5 and < 3 g/24 h)	1.1 (0.5–2.9)	1.1 (0.5–2.1)	1.1 (0.5–2.9)	1.00
Hematuria at baseline, > 5/hpf (%)	30 (68)	13 (72)	17 (65)	0.632
Pyuria at baseline, > 5/hpf (%)	23 (52)	8 (44)	15 (58)	0.387
Casts at baseline, > 1/hpf (%)	9 (20)	2 (11)	7 (27)	0.270
Hypertension at baseline (%)	5 (11)	1 (6)	4 (15)	0.634
ECLAM score at baseline, median (range)	6.5 (2.5–12.5)	6.5 (2.5–9)	6.3 (3.5–12.5)	0.672
Treatment duration, median (range), mo	38 (12–110	47 (28–110)	30 (12–76)	0.002
Treatment duration on stable dose, median (range), mo	30 (12–76)	29 (12–60)	30 (12–76)	0.839
MMF dose*, median (range), g/day	2 (1.2–3)	1.5 (1.2–2)	2 (2–3)	< 0.001
Oral corticosteroid dose**, median (range), mg/day	5.7 (0–15.1)	5 (1.9–9.3)	6 (0–15.1)	0.219
Time to remission, months, median survival time	4	8	4	-/19-†
Time after remission on stable dose, median (range), mo	21 (5–75)	20 (5–55)	24 (9–75)	0.339
Complete remission (%)	32 (73)	12 (67)	20 (77)	0.506
Time to complete remission, months, median survival time	8	9	8	0.857†
Time after complete remission on stable dose, median (range), mo	18 (0–75)	17 (4–40)	19 (0–75)	0.436

* Weighted average dose each patient received taking into consideration the time spent on each drug dosage during the whole followup. ** Average dose each patient received until the end of followup. † Log-rank test. SLE: systemic lupus erythematosus; WHO: World Health Organization; GFR: glomerular filtration rate; hpf: high power field; ECLAM: European Consensus Lupus Activity Measurement; MMF: mycophenolate mofetil.

Table 2. Significant variables for relapse in univariate Cox regression analysis.

Variable	Relapse, N = 16	No Relapse, N = 28	HR	95% CI	p
MMF dose reduction (%)†					
Group 2	6 (23)	20 (77)	1.00	—	—
Group 1	10 (56)	8 (44)	3.37	(1.18–9.69)	0.024
MMF dose, median (range), g/day*†					
Per 0.5-g increase	1.8 (1.3–2)	2 (1.2–3)	0.56	(0.36–0.88)	0.011
Type of initial reduction of MMF dose (%)					
No reduction	6 (23)	20 (77)	1.00	—	—
1.5 g/day or 75% of initial dose	3 (43)	4 (57)	3.21	(1.10–10.76)	0.031
1 g/day or 50% of initial dose	7 (64)	4 (36)	3.44	(1.11–9.26)	0.033
Time from remission to dose reduction (%)					
No reduction	6 (23)	20 (77)	1.00	—	—
≤ 18 mo	7 (88)	1 (130	6.85	(2.21–21.22)	0.001
> 18 mo	3 (30)	7 (70)	1.14	(0.35–3.73)	0.822
Time from complete remission to dose reduction (%)*, N = 32					
No reduction	5 (25)	15 (75)	1.00	—	—
≤ 18 mo	6 (86)	1 (14)	6.29	(1.52–26.07)	0.011
> 18 mo	1 (20)	4 (80)	0.78	(0.13–4.80)	0.788

* Weighted average dose each patient received taking into consideration the time spent on each drug dosage during the whole followup. † Time-dependent analysis. MMF: mycophenolate mofetil; HR: hazard ratio.

(p = 0.001 and p = 0.011, respectively). In contrast, patients tapering therapy later had a risk of relapse similar to that of patients on the stable dosage (Table 2). The relapse rates at different timepoints in association with the time of MMF tapering and the drug dose are shown in Table 3. No association was found between the pace of MMF tapering and renal relapse (Table 2). The occurrence of renal relapse in association with the timing of drug-dose reduction is illustrated in Figure 1A and 1B.

The type of induction treatment used did not influence the disease outcome (HR for relapse was 0.68 for CYC vs MMF treatment; p = 0.453). Further, no significant results emerged comparing the association of baseline patient characteristics, time to remission, achievement of complete remission, and time to this event with renal relapse (data not shown). After adjustment for each of these variables as well as treatment duration, the effect of group, MMF dose, and time from remission to dose reduction remained significant (data not shown).

MMF-related adverse events did not differ significantly between Groups 1 and 2 (p = 0.168; Table 4). The side effects occurred more frequently before the reduction of

Table 3. Disease outcome at different timepoints in association with the time of drug tapering and the drug dose.

Relapse Rate		At 12 or 18 Months, n (%)		At 24 Months, n (%)		At 36 Months, n (%)		At 48 Months, n (%)		At 60 Months, n (%)		At Last Visit, n (%)	
Group 2	2–3 g/day (%)	1 (4)		2 (8)		5 (19)		6 (23)		6 (23)		6 (23)	
Group 1	All patients (%)	0		0		3 (17)		9 (50)		10 (56)		10 (56)	
Time from remission to dose reduction, months													
		≤ 18	> 18	≤ 18	> 18	≤ 18	> 18	≤ 18	> 18	≤ 18	> 18	≤ 18	> 18
Group 1	2 g/day	0/6	0/10	0/4	0/9	0/1	0/5	0/1	0/1	—	—	—	—
	1–1.5 g/day	0/2	—	0/4	0/1	3/7	0/4	7/7	1/6	7/8	1/7	7/8	1/5
	0–0.5 g/day	—	—	—	—	—	0/1	—	1/2	—	2/3	—	2/5
	Total (%)	0	0	0	0	3 (37.5)	0	7 (87.5)	2 (22)	7 (87.5)	3 (30)	7 (87.5)	3 (30)
Patients with complete remission (N = 20 in Group 2; N = 12 in Group 1)													
Group 2	2–3 g/day (%)	1 (5)		2 (10)		4 (20)		5 (25)		5 (25)		5 (25)	
Group 1	All patients (%)	0		0		2 (17)		7 (58)		7 (58)		7 (58)	
Time from complete remission to dose reduction, months													
		≤ 18	> 18	≤ 18	> 18	≤ 18	> 18	≤ 18	> 18	≤ 18	> 18	≤ 18	> 18
Group 1	2 g/day	0/5	0/5	0/3	0/4	0/1	0/3	—	—	—	—		
	1–1.5 g/day	0/2	—	0/4	0/1	2/6	0/2	6/7	0/3	6/7	0/3	6/6	0/2
	0–0.5 g/day	—	—	—	—	—	—	—	1/2	—	1/2	0/1	1/3
	Total (%)	0	0	0	0	2 (29)	0	6 (86)	1 (20)	6 (86)	1 (20)	6 (86)	1 (20)

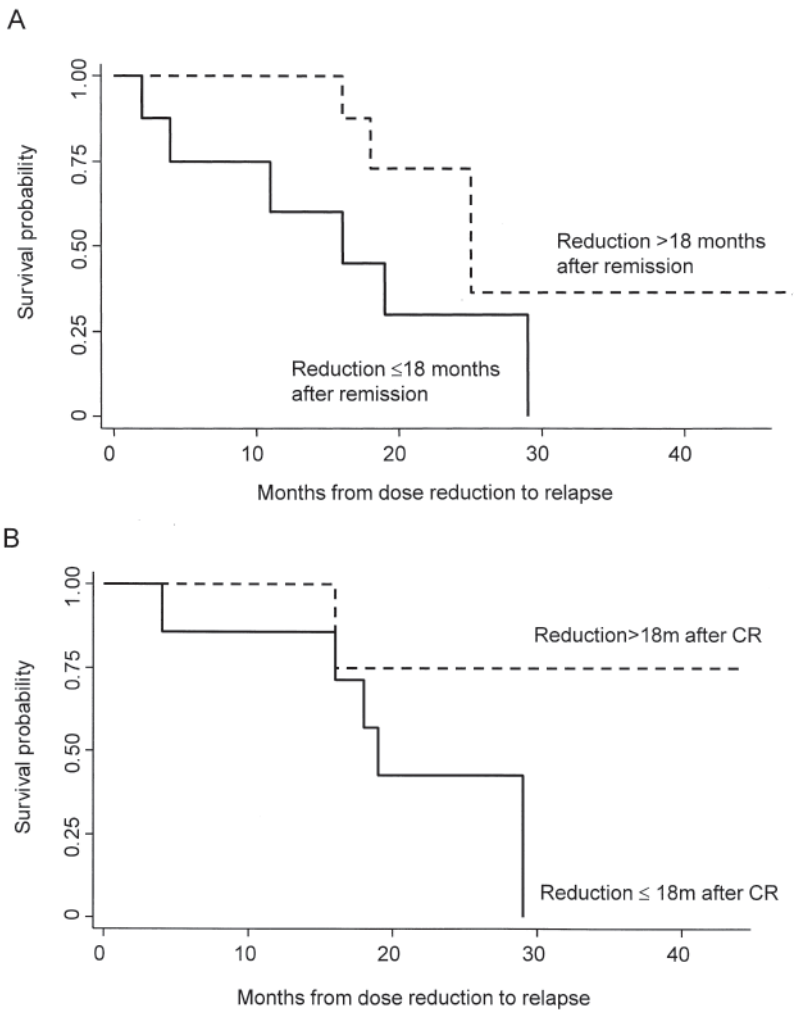

Figure 1. A. Kaplan-Meier curve for renal relapse after reduction of MMF depending on the time from remission to dose tapering in the 18 patients of Group 1; p = 0.031 for ≤ 18 months vs > 18 months (log-rank test). B. Kaplan-Meier curve for renal relapse after reduction of MMF depending on the time from complete remission (CR) to dose tapering in the 18 patients of Group 1; p = 0.05 for ≤ 18 months vs > 18 months (log-rank test). m: months.

MMF in Group 1 (in 8/10 vs 2/10 patients). Drug toxicity was not associated with the duration of treatment (OR 1.01 per 1-year increase, p = 0.390).

DISCUSSION

To date, prospective controlled studies to investigate whether MMF therapy can be safely discontinued in patients with quiescent lupus nephritis have not been carried out. In previous studies assessing the efficacy of MMF as either longterm induction-maintenance or maintenance therapy for proliferative lupus nephritis, reduction of MMF dose has been tried in responders or in case of intolerance[1,3,4,5]. Most flares in these studies have been reported to occur when medication was reduced[4,5].

In our study, despite no drug tapering in Group 2, a considerable percentage of patients developed renal flares within a relatively short median followup of 30 months, and this was comparable to reports in the literature (23% vs 15%)[1]. In contrast, patients reducing MMF experienced disease flares more frequently than in previous studies with a similar observation time: 56% vs 34% at approximately 4 years of followup[4]. Our data showed that the time of drug reduction may be critical for the occurrence of relapse. Reducing MMF > 1.5 years after remission/complete remission results in similar relapse rates compared to patients receiving the stable drug dose, and accounts for fewer medication-related adverse events. On the other hand, premature reduction of the drug was associated with disease exacerbations in the majority of cases. Whether continuation of MMF at a low dosage in responders is superior to complete withdrawal of therapy remains to be determined.

Our results are in accord with the limited number of stud-

Table 4. MMF-related side effects in patients.

Group 1, 56% (10/18)	Group 2, 36% (9/26)
Before MMF dose reduction, n = 8	
3 herpes zoster virus infections	1 chlamydia-related myocarditis
1 salmonella species gastroenteritis	1 ulcerative gastritis
2 diarrhea that remitted after tapering of MMF	1 gastrointestinal discomfort that resolved after reducing MMF from 3 to 2 g/day
2 hypercholesterolemia	
After MMF dose reduction, n = 2	1 alopecia
1 human papilloma virus	5 hypercholesterolemia
1 Epstein-Barr virus infection	

MMF: mycophenolate mofetil.

ies assessing the possibility of therapy withdrawal in patients with quiescent systemic lupus erythematosus treated with CYC[9,10]. In line with our observations, 12–19 month duration of therapy after remission has also been reported to be effective in preventing relapse[9].

Our study is based on a retrospective analysis of patient data. The heterogeneity in the timing and rate of MMF dose-tapering is a drawback. However, this allowed evaluation of the association between the disease outcome and tapering of the drug at different timepoints. Although the decision to reduce MMF was based on the absence of disease activity in all cases, we cannot exclude potential bias among the treating physicians. In addition, although the entire median followup of patients who experienced a drug dose reduction was 4 years, the median duration of therapy after drug reduction was 18.5 months. Finally, the limited number of patients did not allow application of multivariate models. Thus, larger controlled trials should be carried out to assess the safety of therapy tapering or withdrawal in the very long term.

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