

EFFICACY OF MYCOPHENOLATE MOFETIL IN PATIENTS WITH DIFFUSE PROLIFERATIVE LUPUS NEPHRITIS

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ABSTRACT

Background The combination of cyclophosphamide and prednisolone is effective for the treatment of severe lupus nephritis but has serious adverse effects. Whether mycophenolate mofetil can be substituted for cyclophosphamide is not known.

Methods In 42 patients with diffuse proliferative lupus nephritis we compared the efficacy and side effects of a regimen of prednisolone and mycophenolate mofetil given for 12 months with those of a regimen of prednisolone and cyclophosphamide given for 6 months, followed by prednisolone and azathioprine for 6 months. Complete remission was defined as a value for urinary protein excretion that was less than 0.3 g per 24 hours, with normal urinary sediment, a normal serum albumin concentration, and values for serum creatinine and creatinine clearance that were no more than 15 percent above the base-line values. Partial remission was defined as a value for urinary protein excretion that was between 0.3 and 2.9 g per 24 hours, with a serum albumin concentration of at least 3.0 g per deciliter.

Results Eighty-one percent of the 21 patients treated with mycophenolate mofetil and prednisolone (group 1) had a complete remission, and 14 percent had a partial remission, as compared with 76 percent and 14 percent, respectively, of the 21 patients treated with cyclophosphamide and prednisolone followed by azathioprine and prednisolone (group 2). The improvements in the degree of proteinuria and the serum albumin and creatinine concentrations were similar in the two groups. One patient in each group discontinued treatment because of side effects. Infections were noted in 19 percent of the patients in group 1 and in 33 percent of those in group 2 ($P=0.29$). Other adverse effects occurred only in group 2; they included amenorrhea (in 23 percent of the patients), hair loss (19 percent), leukopenia (10 percent), and death (10 percent). The rates of relapse were 15 percent and 11 percent, respectively.

Conclusions For the treatment of diffuse proliferative lupus nephritis, the combination of mycophenolate mofetil and prednisolone is as effective as a regimen of cyclophosphamide and prednisolone followed by azathioprine and prednisolone. (N Engl J Med 2000;343:1156-62.)

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IMMUNOSUPPRESSIVE regimens of glucocorticoids combined with cytotoxic drugs, particularly cyclophosphamide, are effective for the treatment of severe proliferative lupus nephritis.¹⁻³ However, cyclophosphamide has immediate and cumulative adverse effects, such as marrow suppression, gonadal toxicity, and hemorrhagic cystitis, and it is associated with an increased risk of cancer.

Mycophenolic acid, the active metabolite of mycophenolate mofetil, selectively suppresses the proliferation of T and B lymphocytes, the formation of antibodies, and the glycosylation of adhesion molecules by inhibiting purine nucleotide synthesis and depleting lymphocytes and monocytes of guanosine triphosphate.⁴ Mycophenolate mofetil is more effective than azathioprine in preventing acute rejection of renal allografts.⁵ Its adverse effects also compare favorably with those of cyclophosphamide, with gastrointestinal upset being the most common,⁶ and it has no mutagenic effects.⁴ The results of studies in animals and anecdotal clinical reports suggest that mycophenolate mofetil might have a role in the treatment of patients with lupus nephritis.⁷⁻¹⁰ We evaluated the efficacy and safety of mycophenolate mofetil combined with prednisolone for the treatment of severe lupus nephritis, as compared with prednisolone combined first with cyclophosphamide and then with azathioprine — a regimen associated with rates of complete and partial remission of 77 percent and 23 percent, respectively.¹¹

METHODS

Patients

Between November 1996 and October 1998, we studied 42 patients who had systemic lupus erythematosus according to the criteria of the American Rheumatism Association, including renal-biopsy evidence of diffuse proliferative lupus nephritis (class IV according to the World Health Organization's classification system),¹² urinary protein excretion of 1 g or more per 24 hours, and a serum albumin concentration of 3.5 g per deciliter or less. Patients with a serum creatinine concentration higher than 3.4 mg per deciliter (300 μ mol per liter) were excluded, as were those

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with life-threatening complications such as cerebral lupus or severe infection, those with a history of poor compliance with drug regimens, and women who were pregnant or unwilling to use contraception. Patients who had received cyclophosphamide within the previous six months or who had taken oral prednisolone at a dose of 0.8 mg per kilogram of body weight per day or more for more than two weeks were also excluded. The study was approved by the ethics committees of the University of Hong Kong and the participating hospitals, and all patients gave written informed consent.

Renal-biopsy specimens were examined by light, immunofluorescence, and electron microscopy, and the findings were categorized according to standard methods.¹³ Patients whose specimens showed superimposed membranous changes were included in the study, provided that there were concomitant diffuse proliferative features. Investigators who were unaware of the treatment assignments subsequently evaluated the renal-biopsy specimens according to indexes of disease activity and chronicity.¹⁴

Immunosuppressive Treatment and Study Protocol

Within 48 hours after undergoing renal biopsy, the patients were randomly assigned to receive one of two treatments: oral mycophenolate mofetil plus oral prednisolone (group 1) or oral cyclophosphamide plus oral prednisolone (group 2). The mycophenolate mofetil was started at a dose of 1 g twice a day, the cyclophosphamide at a dose of 2.5 mg per kilogram per day, and prednisolone at 0.8 mg per kilogram per day. The doses of mycophenolate mofetil and cyclophosphamide were not changed during the first six months unless the drugs had adverse effects. The daily dose of prednisolone was reduced by 5 mg per day every two weeks until the dose was 20 mg per day, after which it was reduced by 2.5 mg per day every two weeks for four weeks and then by 2.5 mg per day every four weeks, until a maintenance dose of 10 mg per day had been reached, at approximately six months. The dose of mycophenolate mofetil was halved at six months. In group 2, cyclophosphamide was replaced by azathioprine (1.5 mg per kilogram per day given orally) at six months. After 12 months, mycophenolate mofetil was replaced by azathioprine (1 mg per kilogram per day, given orally) in group 1, and in group 2 the dose of azathioprine was reduced to 1 mg per kilogram per day.

The criteria for the discontinuation of treatment included any of the following: leukopenia (white-cell count, <2000 per cubic millimeter), thrombocytopenia (platelet count, <50,000 per cubic millimeter), a hemoglobin concentration of less than 8 g per deciliter, an increase in the serum creatinine concentration with or without a concomitant rise in the serum anti-double-stranded DNA antibody or a fall in the C3 concentration after two weeks of treatment or failure of the serum anti-double-stranded DNA antibody to fall or the C3 concentration to rise after four weeks, a doubling of the serum creatinine concentration, life-threatening complications (e.g., cerebral lupus or severe infection), pregnancy, severe gastrointestinal upset despite a reduction in the dose of mycophenolate mofetil (in group 1), or poor compliance. In patients with mild leukopenia (white-cell count, 2000 to 4000 per cubic millimeter) or thrombocytopenia (platelet count, 50,000 to 100,000 per cubic millimeter), the dose of mycophenolate mofetil or cyclophosphamide was halved. Mild gastrointestinal upset in patients in group 1 was treated by reducing the dose of mycophenolate mofetil by 50 percent and then gradually increasing it by the same amount.

The duration of the study was 12 months. Patients were seen weekly for four weeks, then every other week for eight weeks, and then monthly. At each follow-up visit, we evaluated the patients for clinical manifestations of lupus nephritis and for any adverse effects of therapy. Blood pressure was measured, urinalysis was performed, renal and liver function were evaluated, and serum anti-double-stranded DNA antibodies and serum C3 were measured. Urinary protein excretion was measured in 24-hour samples obtained every other week during the first month, then monthly

for 3 months and at 6, 9, and 12 months. Creatinine clearance was measured at 6 and 12 months. Hypertension was treated with a calcium-channel blocker, and a beta blocker was added if necessary. The target systolic blood pressure was less than 150 mm Hg and the target diastolic pressure less than 90 mm Hg. Angiotensin-converting-enzyme inhibitors and angiotensin II-receptor antagonists were not used because of their possible effects on urinary protein and renal function. Prophylaxis with isoniazid (300 mg per day given orally) was prescribed for patients with a history of clinical or radiologic evidence of tuberculosis.

Complete remission was defined as a value for urinary protein excretion that was less than 0.3 g per 24 hours, with normal urinary sediment, a normal serum albumin concentration, and values for both serum creatinine and creatinine clearance that were 15 percent or less above the base-line values. Partial remission was defined as a value for urinary protein excretion that was between 0.3 and 2.9 g per 24 hours, with a serum albumin concentration of at least 3.0 g per deciliter and stable renal function. Treatment failure

TABLE 1. CHARACTERISTICS OF 42 PATIENTS WITH DIFFUSE PROLIFERATIVE LUPUS NEPHRITIS, ACCORDING TO THE ASSIGNED TREATMENT.*

CHARACTERISTIC	GROUP 1 (N=21)	GROUP 2 (N=21)
Sex — M/F	1/20	2/19
Age — yr	36±11	39±9
Duration of lupus — mo	72±69	97±80
Duration of nephritis — mo	54±63	77±76
Organ involvement — no. (%)		
Skin	13 (62)	9 (43)
Joint	15 (71)	12 (57)
Serous membrane	5 (24)	5 (24)
Serum creatinine — mg/dl†	1.2±0.6	1.2±0.3
Creatinine clearance — ml/min/1.73 m ² of body-surface area	86±35	77±31
Urinary protein excretion — g/24 hr	5.8±4.6	3.7±1.7
Serum albumin — g/dl‡	2.8±0.6	2.8±0.5
Serum C3 — mg/dl§	62±34	46±20
Serum anti-double-stranded DNA antibody — IU/ml¶	293±204	426±627
Activity score	8.6±2.8	8.6±1.8
Chronicity score**	2.8±1.1	3.9±3.0

*Patients in group 1 received mycophenolate mofetil with prednisolone for 12 months. Patients in group 2 received cyclophosphamide with prednisolone for six months, followed by azathioprine with prednisolone for six months. Plus-minus values are means ±SD. P>0.05 for all comparisons between the two groups.

†The normal range for creatinine is 0.93 to 1.43 mg per deciliter. To convert the values to micromoles per liter, multiply by 88.4.

‡The normal range for serum albumin is 4.2 to 5.4 g per deciliter.

§The normal range for serum C3 is 60 to 130 mg per deciliter.

¶The normal range for serum anti-double-stranded DNA antibody is 0 to 35 IU per milliliter.

||The score on the activity index was the sum of the scores (on a scale of 1 to 3) for endocapillary proliferation, karyorrhexis and fibrinoid necrosis (with the score multiplied by 2), cellular crescents (with the score multiplied by 2), hyaline deposits, leukocyte exudation, and interstitial inflammation.¹⁴ Higher scores indicate greater disease activity; the highest possible score is 24.

**The score on the chronicity index was the sum of the scores (on a scale of 1 to 3) for glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis.¹⁴ Higher scores indicate greater chronicity; the highest possible score is 12.

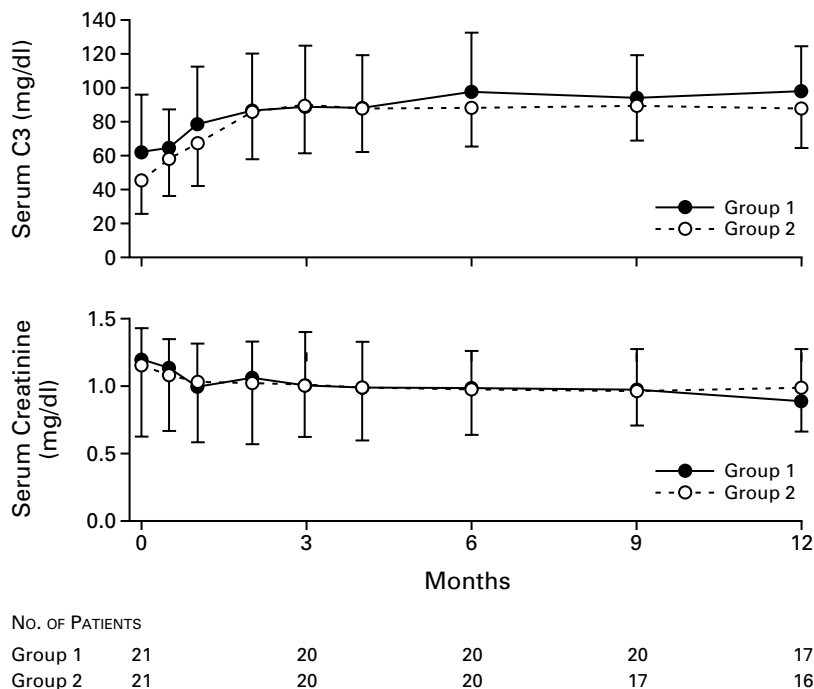


Figure 1. Mean (\pm SD) Serum C3 and Creatinine Concentrations in Patients with Diffuse Proliferative Lupus Nephritis Who Were Treated with Mycophenolate Mofetil and Prednisolone (Group 1) or with Cyclophosphamide and Prednisolone Followed by Azathioprine and Prednisolone (Group 2).

In both groups, the mean serum C3 concentration after two weeks of therapy was significantly higher than the base-line value, and it remained significantly higher at each subsequent evaluation ($P < 0.05$ for all comparisons between base-line and follow-up in each group). The mean serum creatinine concentration was significantly lower than the base-line value after 2 weeks of therapy in group 2 and after 12 weeks of therapy in group 1, and it remained significantly lower at each subsequent evaluation ($P < 0.05$). The numbers below the panels are numbers of patients for whom data were available. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

was defined as a value for urinary protein excretion that remained at or above 3 g per 24 hours or a value of 0.3 to 2.9 g per 24 hours but with a serum albumin concentration of less than 3.0 g per deciliter, an increase in the serum creatinine concentration greater than or equal to 0.6 mg per deciliter (50 μ mol per liter), or a value for creatinine clearance that was more than 15 percent above the base-line value, or the discontinuation of treatment due to side effects.

For patients with a complete or partial remission, renal biopsy was repeated if urinary protein excretion increased by 1 g per 24 hours or more over the base-line value or if there was an increase in the serum creatinine concentration, irrespective of the value for the serum anti-double-stranded DNA antibody or C3 concentration. Renal relapse was confirmed by histologic studies. Clinical status was reviewed and categorized at the coordinating center by personnel who had no knowledge of the treatment assignment.

End Points

The incidence of complete remission was the primary end point with respect to efficacy in this study. Predefined secondary end points included partial remission, adverse effects (including infections, amenorrhea, and hair loss), a doubling of the serum creatinine concentration, a relapse of lupus, and death.

Statistical Analysis

Serial data were compared within and between groups by repeated-measures analysis of variance with one between-group fac-

tor and one repeated-measures factor. Unpaired t-tests were used for between-group comparisons, and paired t-tests were used for within-group comparisons. The results are reported as differences between mean values with 95 percent confidence intervals. The values for C3, anti-double-stranded DNA antibodies, and creatinine were transformed logarithmically before analysis, and the results are presented as the ratio of geometric means with 95 percent confidence intervals. Categorical groups were compared by the chi-square test and Fisher's exact test, as appropriate. McNemar's test was used for comparisons of dichotomous variables before and after treatment. All statistical tests were two-sided.

RESULTS

There were 21 patients in each group. In 16 of the patients in group 1 and in 13 of those in group 2, the diagnosis of systemic lupus erythematosus was new. The base-line characteristics of the patients in the two groups were similar (Table 1). A total of 29 patients (69 percent) had low serum C3 concentrations, and 35 (83 percent) had high serum anti-double-stranded DNA antibody concentrations. Twelve patients (7 in group 1 and 5 in group 2) had high serum creatinine concentrations ($P = 0.50$), and 15 (8 in group 1 and 7 in group 2) had a creatinine clear-

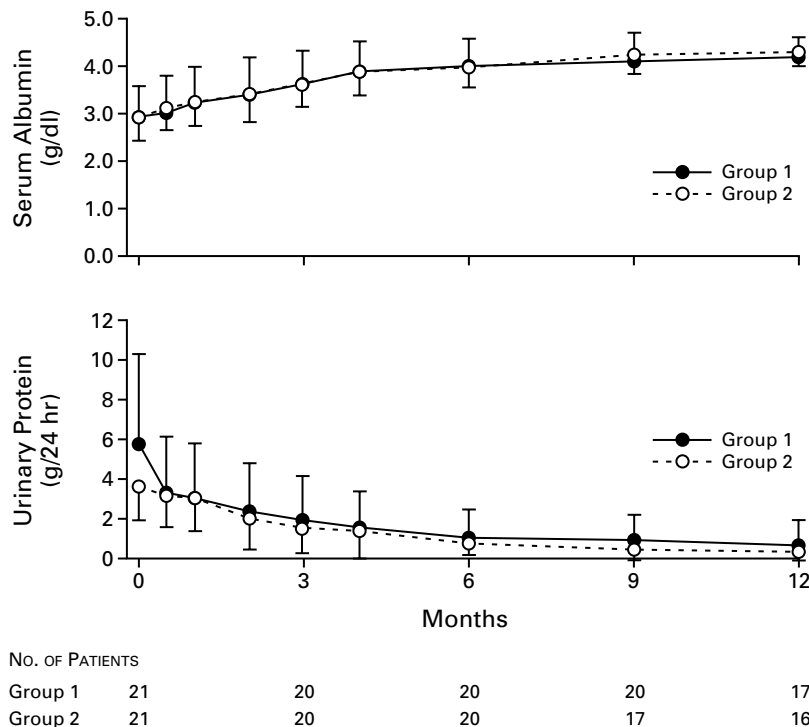


Figure 2. Mean (\pm SD) Serum Albumin Concentration and Urinary Protein Excretion in Patients with Diffuse Proliferative Lupus Nephritis Who Were Treated with Mycophenolate Mofetil and Prednisolone (Group 1) or with Cyclophosphamide and Prednisolone Followed by Azathioprine and Prednisolone (Group 2).

The mean serum albumin concentration was significantly higher than the base-line value after two weeks of therapy in group 2 and after four weeks of therapy in group 1, and it remained significantly higher at each subsequent evaluation ($P < 0.05$ for the comparisons in each group). Urinary protein excretion was significantly lower than the base-line value after two weeks of therapy in group 1 and after four weeks of therapy in group 2, and it remained significantly lower at each subsequent evaluation ($P < 0.05$ for the comparisons in each group). The numbers below the panels are numbers of patients for whom data were available.

ance that was less than 80 ml per minute per 1.73 m² of body-surface area ($P = 0.75$). Diffuse membranous deposits were noted in biopsy specimens from three patients in each group.

Outcome of Treatment

The mean serum C3 concentration increased significantly in both groups after two weeks of treatment (Fig. 1). The proportion of patients with low serum C3 concentrations was reduced from 57 percent at base line to 10 percent at eight weeks in group 1 ($P = 0.002$) and from 90 percent to 57 percent in group 2 ($P = 0.01$); the proportion of patients with high serum anti-double-stranded DNA antibody concentrations was reduced from 81 percent to 10 percent in group 1 ($P = 0.001$) and from 76 percent to 52 percent in group 2 ($P = 0.03$). The differences between the proportions of patients with abnormal values in the two groups at eight weeks were not significant.

Serial values for serum C3, albumin, and creatinine concentrations and for urinary protein excretion were similar in the two groups (Fig. 1 and 2), as were the concentrations of anti-double-stranded DNA antibody. The mean serum creatinine concentration decreased after 2 weeks of treatment in group 2 (ratio of geometric mean at base line to geometric mean at two weeks, 1.1; 95 percent confidence interval, 1.0 to 1.2; $P = 0.04$) and after 12 weeks of treatment in group 1 (ratio of geometric mean, 1.1; 95 percent confidence interval, 1.0 to 1.2; $P = 0.03$). Urinary protein excretion decreased and the serum albumin concentration increased within four weeks in both groups. At 12 months, creatinine clearance did not differ significantly from the base-line value in either group, and the earlier improvements in urinary protein excretion and the serum C3, albumin, and creatinine concentrations were sustained; all these values were similar in the two groups (Table 2). At 12 months, none of the patients had a serum creatinine

TABLE 2. LABORATORY VALUES AT BASE LINE AND AT 12 MONTHS, ACCORDING TO THE ASSIGNED TREATMENT.*

VARIABLE	BASE LINE	12 MONTHS	DIFFERENCE OR RATIO (95% CI)	P VALUE
Serum C3 (mg/dl)				
Group 1	54.1	93.1	0.58 (0.6 to 0.8)	0.001
Group 2	46.4	85.7	0.54 (0.5 to 0.6)	<0.001
Serum albumin (g/dl)				
Group 1	2.8±0.6	4.0±0.4	1.2±0.6 (0.8 to 1.4)	<0.001
Group 2	2.8±0.5	4.1±0.3	1.3±0.4 (1.0 to 1.5)	<0.001
Serum creatinine (mg/dl)†				
Group 1	1.13	0.97	1.16 (1.04 to 1.37)	0.02
Group 2	1.10	0.99	1.11 (1.06 to 1.38)	0.01
Urinary protein excretion (g/24 hr)				
Group 1	5.8±4.6	0.5±1.1	-5.3±2.4 (-2.4 to -6.3)	<0.001
Group 2	3.7±1.7	0.2±0.3	-3.5±1.1 (-2.4 to -4.1)	<0.001
Creatinine clearance (ml/min/1.73 m ²)				
Group 1	86±35	92±21	6±28 (-15 to 18)	0.15
Group 2	77±31	82±39	5±37 (-22 to 11)	0.18

*Patients in group 1 received mycophenolate mofetil with prednisolone for 12 months. Patients in group 2 received cyclophosphamide with prednisolone for six months, followed by azathioprine with prednisolone for six months. Values for serum albumin, urinary protein excretion, and creatinine clearance are means ±SD, with the difference between the values at base line and 12 months given. Values for serum C3 and creatinine are geometric means, with the ratio of the base-line value to the value at 12 months given. P>0.05 for all comparisons between group 1 and group 2. CI denotes confidence interval.

†To convert the values for creatinine to micromoles per liter, multiply by 88.4.

TABLE 3. OUTCOME OF TREATMENT.*

VARIABLE	GROUP 1 (N=21)		GROUP 2 (N=21)		DIFFERENCE BETWEEN GROUPS†	P VALUE
	no.	% (95% CI)	no.	% (95% CI)		
Complete remission	17	81 (58 to 95)	16	76 (53 to 92)	5 (-20 to 30)	1.00
Partial remission	3	14	3	14	0 (-21 to 21)	1.00
Treatment failure	1	5	2	10	-5 (-20 to 11)	1.00
Relapse‡	3	15	2	11	4 (-16 to 25)	1.00
Discontinuation of treatment	1	5	1	5	0 (-13 to 13)	1.00
Death	0		2	10	-10 (-22 to 3)	0.49
	wk after diagnosis				wk (95% CI)	
Time to complete remission		17±11		22±11	-5 (-13 to 2)	0.15
Time to partial remission		16±14		14±3	2 (-28 to 32)	0.81
Time to relapse§		37, 42, 42		36, 42	1.3 (-8.5 to 11.2)	0.70

*Patients in group 1 received mycophenolate mofetil with prednisolone for 12 months. Patients in group 2 received cyclophosphamide with prednisolone for six months, followed by azathioprine with prednisolone for six months. Plus-minus values are means ±SD. CI denotes confidence interval.

†The difference is shown as the value for group 1 minus the value for group 2.

‡Data were available for 20 patients in group 1 and 19 in group 2.

§Values are for individual patients. The difference between the groups is the mean value.

concentration that was more than 15 percent above the base-line value.

The incidence of complete or partial remission and the duration of treatment before a complete remission was achieved were similar in the two groups (Table 3). The base-line characteristics of the patients who

subsequently had a complete or partial remission were similar, including the values for the activity index and the chronicity index. All the patients with a partial remission had a base-line value for urinary protein excretion that was higher than 3.0 g per 24 hours (range, 3.1 to 20.2). At four weeks, the mean (±SD)

value for urinary protein excretion was 2.4 ± 2.0 g per 24 hours in the group of patients who had a complete remission and 5.1 ± 3.1 g per 24 hours in the group with a partial remission, a difference of 2.7 g per 24 hours (95 percent confidence interval, 0.7 to 4.7; $P=0.01$). After four months of treatment, the serum albumin concentration was 3.8 ± 0.4 g per deciliter in the complete-remission group and 3.2 ± 0.8 g per deciliter in the partial-remission group, a difference of 0.6 g per deciliter (95 percent confidence interval, 0.2 to 1.0; $P=0.01$).

Of the 39 patients who had a complete or partial remission, 3 (15 percent) in group 1 and 2 (11 percent) in group 2 had relapses (Table 3), which occurred after nine months, when the patients were receiving maintenance immunosuppressive therapy. Repeated biopsy revealed focal proliferative lupus nephritis in two patients, diffuse proliferative lupus nephritis in one patient, and membranous lupus nephritis in two patients.

Cessation of Treatment and Adverse Effects

Treatment was discontinued prematurely in two patients: one in group 1 at three weeks because of diarrhea and one in group 2 at four weeks because of leukopenia. In addition, one patient in group 2 died at 11 weeks without having had a response to treatment. The study treatment was classified as having failed in these three patients. Leukopenia (white-cell count, ≤ 4000 per cubic millimeter) occurred in two patients in group 2, in one of whom treatment was discontinued. The condition of the other patient improved after the dose of cyclophosphamide was reduced. Infections developed in 11 patients (26 percent), with a similar incidence in the two groups (Table 4); 3 of the 6 episodes (50 percent) in group 1 and 6 of the 10 episodes (60 percent) in group 2 necessitated hospitalization. One episode of pneumonia, in a patient in group 2, was associated with leukopenia. One patient in group 1 had severe diarrhea. There were no significant differences in the incidence of hair loss or amenorrhea between the two groups. Two patients (both in group 2) died during the study: one from miliary tuberculosis and the adult respiratory distress syndrome at 11 weeks and the other from cerebral hemorrhage, which was unrelated to thrombocytopenia or hypertension, at 28 weeks.

DISCUSSION

Data from the National Institutes of Health have shown that patients with lupus nephritis who are treated with glucocorticoids and a prolonged course of cytotoxic agents have better long-term renal function than those treated with glucocorticoids alone.¹⁵ Active lupus is characterized by the activation of lymphocytes and the production of autoantibodies. Unlike cyclophosphamide, which is a nonspecific cytotoxic drug, mycophenolate mofetil suppresses lymphocyte

TABLE 4. ADVERSE EFFECTS.*

ADVERSE EFFECT	GROUP 1 (N=21)		GROUP 2 (N=21)		P VALUE
	no.	% (95% CI)	no.	% (95% CI)	
Infection	4	19 (5–42)	7	33 (15–57)	0.29
No. of episodes	6		10		0.45
Type					
Respiratory infection†	4	67	5	50	0.63
Tuberculosis	0		1	10	1.00
Urinary tract infection	0		2	20	0.50
Herpes zoster	2	33	2	20	0.60
Other					
Leukopenia	0		2	10	0.49
Hair loss	0		4	19	0.11
Amenorrhea‡	0		3	23	0.09
Transient	0		2	15	0.21
Permanent	0		1	8	0.46
Diarrhea	1	5	0		1.00
Death	0		2	10	0.49

*Patients in group 1 received mycophenolate mofetil with prednisolone for 12 months. Patients in group 2 received cyclophosphamide with prednisolone for six months, followed by azathioprine with prednisolone for six months. With the exception of the number of episodes and type of infection, numbers refer to numbers of patients.

†Data were available for 6 patients in group 1 and 10 in group 2.

‡There were 15 premenopausal patients in group 1 and 13 in group 2.

proliferation selectively because of the dependence of these cells on purine nucleotide synthesis. The effect of mycophenolate mofetil in depleting lymphocytes of guanosine triphosphate and suppressing glycosylation of adhesion molecules may provide an additional clinical benefit.⁴

Optimal treatment of lupus nephritis entails rapid induction of remission, effective prophylaxis against relapse, and prevention of renal failure. Progressive renal failure, a common end point in previous studies, has been reported in up to 25 percent of patients within five years after diagnosis, even after treatment with prednisolone and intravenous cyclophosphamide.^{2,3,15} Indeed, treatment-related differences in rates of renal failure may not be discernible early in the course of treatment. We therefore chose complete remission as the primary end point in our one-year study, since the purpose of the study was to compare the efficacy of the immunosuppressive regimens in controlling acute disease activity. Control of disease activity is important in order to preserve functional renal tissue and prevent renal failure. We defined complete remission strictly, as the normalization of values for urinary protein excretion, urinary sediment, and serum albumin and a stable serum creatinine concentration. The long-term renal outcome represents the additive effect of multiple confounding factors, including the efficacy of immunosuppressive therapy; preexisting renal reserve and scarring; the number, severity, and treatment of subsequent relapses of nephritis; and the adequacy of blood-pressure control.

With regard to the last factor, we made sure that blood-pressure control was satisfactory and similar in the two treatment groups.

We found that the regimen of mycophenolate mofetil and prednisolone induced complete remission in 81 percent of patients and partial remission in 14 percent within 12 months. These results were similar to those obtained with our sequential regimen but were better than the response rates reported by other investigators.^{2,3} The more favorable response in our study may be attributable to earlier diagnosis and treatment, as evidenced by the lower indexes of chronicity.¹¹ Whether a patient had a complete or partial remission was not related to base-line characteristics, except that all patients with partial remission had nephrotic-range proteinuria at base line. Improvements in urinary protein excretion, serum albumin concentrations, and renal function were sustained at 12 months, and none of the patients had a deterioration in renal function, which might precede progressive renal failure on more prolonged follow-up. In view of the severe disease in our patients, as indicated by a mean disease-activity score of 8.6 and the fact that 29 percent of the patients had abnormal serum creatinine concentrations, the results of treatment with mycophenolate mofetil compare favorably with those of conventional therapies.

With regard to side effects, severe diarrhea developed in only one patient treated with mycophenolate mofetil, and the incidence of infection was similar in the two treatment groups. These results suggest that mycophenolate mofetil is easier to tolerate than cyclophosphamide, since hair loss, amenorrhea, and death occurred only in the group of patients treated with cyclophosphamide.

Fifteen percent of the patients treated with mycophenolate mofetil had a relapse within the first year. Although this rate of relapse was similar to the rate in group 2 and the rate among patients treated with intravenous cyclophosphamide for six months,² the sample in our study was too small for a meaningful evaluation of differences. In view of the fact that mycophenolate mofetil is tolerable and not mutagenic, a higher maintenance dose (e.g., 1.5 g per day) might reduce the risk of relapse.

We conclude that mycophenolate mofetil combined with prednisolone is an effective treatment for patients with diffuse proliferative lupus nephritis, with

results and toxicity that are similar to those of treatment with cyclophosphamide followed by azathioprine.

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APPENDIX

Other members of the Hong Kong–Guangzhou Nephrology Study Group are as follows: *University of Hong Kong and Queen Mary Hospital, Hong Kong, China* — S.C.W. Tang, L.S.L. Lui, M.F. Lam, C.C.K. Ho, and C.C. Mok; *Sun Yat Sen University of Medical Sciences First Affiliated Hospital, Guangzhou, China* — Z.P. Jiang, Y.J. Li, T. Jang, R.G. Ye, and X.Q. Yu; *Kwong Wah Hospital, Hong Kong, China* — S.K. Mak; and *Princess Margaret Hospital, Hong Kong, China* — W.K. Tsang.

REFERENCES

1. Donadio JV Jr, Holley KE, Ferguson RH, Ilstrup DM. Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. *N Engl J Med* 1978;299:1151-5.
2. Boumpas DT, Austin HA III, Vaughn EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992;340:741-5.
3. Lewis EJ, Hunsicker LG, Lan S-P, Rohde RD, Lachin JM. A controlled trial of plasmapheresis in severe lupus nephritis. *N Engl J Med* 1992;326:1373-9.
4. Allison AC, Eugui EM. Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). *Clin Transplant* 1996;10:77-84.
5. Halloran P, Mathew T, Tomlanovich S, Groth C, Hoofman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation* 1997;63:39-47. [Erratum, *Transplantation* 1997;63:618.]
6. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995;345:1321-5.
7. Jonsson CA, Svensson L, Carlsten H. Beneficial effect of the inosine monophosphate dehydrogenase inhibitor mycophenolate mofetil on survival and severity of glomerulonephritis in systemic lupus erythematosus (SLE)-prone MRL1pr/1pr mice. *Clin Exp Immunol* 1999;116:534-41.
8. Van Bruggen MC, Walgreen B, Rijke TP, Berden JH. Attenuation of murine lupus nephritis by mycophenolate mofetil. *J Am Soc Nephrol* 1998;9:1407-15.
9. Dooley MA, Cosio FG, Nachman PH, et al. Mycophenolate mofetil therapy in lupus nephritis: clinical observations. *J Am Soc Nephrol* 1999;10:833-9.
10. Glicklich D, Acharya A. Mycophenolate mofetil therapy for lupus nephritis refractory to intravenous cyclophosphamide. *Am J Kidney Dis* 1998;32:318-22.
11. Chan TM, Li FK, Wong RWS, Wong KL, Chan KW, Cheng IKP. Sequential therapy for diffuse proliferative and membranous lupus nephritis: cyclophosphamide and prednisolone followed by azathioprine and prednisolone. *Nephron* 1995;71:321-7.
12. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
13. Churg J, Sobin LH, eds. *Renal disease: classification and atlas of glomerular diseases*. Tokyo: Igaku-Shoin, 1982.
14. Austin HA III, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. *Kidney Int* 1984;25:689-95.
15. Austin HA III, Klippel JH, Balow JE, et al. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986;314:614-9.