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Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

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ABSTRACT

BACKGROUND

Since anecdotal series and small, prospective, controlled trials suggest that mycophenolate mofetil may be effective for treating lupus nephritis, larger trials are desirable.

METHODS

We conducted a 24-week randomized, open-label, noninferiority trial comparing oral mycophenolate mofetil (initial dose, 1000 mg per day, increased to 3000 mg per day) with monthly intravenous cyclophosphamide (0.5 g per square meter of body-surface area, increased to 1.0 g per square meter) as induction therapy for active lupus nephritis. A change to the alternative regimen was allowed at 12 weeks in patients who did not have an early response. The study protocol specified adjunctive care and the use and tapering of corticosteroids. The primary end point was complete remission at 24 weeks (normalization of abnormal renal measurements and maintenance of baseline normal measurements). A secondary end point was partial remission at 24 weeks.

RESULTS

Of 140 patients recruited, 71 were randomly assigned to receive mycophenolate mofetil and 69 were randomly assigned to receive cyclophosphamide. At 12 weeks, 56 patients receiving mycophenolate mofetil and 42 receiving cyclophosphamide had satisfactory early responses. In the intention-to-treat analysis, 16 of the 71 patients (22.5 percent) receiving mycophenolate mofetil and 4 of the 69 patients receiving cyclophosphamide (5.8 percent) had complete remission, for an absolute difference of 16.7 percentage points (95 percent confidence interval, 5.6 to 27.9 percentage points; P=0.005), meeting the prespecified criteria for noninferiority and demonstrating the superiority of mycophenolate mofetil to cyclophosphamide. Partial remission occurred in 21 of the 71 patients (29.6 percent) and 17 of the 69 patients (24.6 percent), respectively (P=0.51). Three patients assigned to cyclophosphamide died, two during protocol therapy. Fewer severe infections and hospitalizations but more diarrhea occurred among those receiving mycophenolate.

CONCLUSIONS

In this 24-week trial, mycophenolate mofetil was more effective than intravenous cyclophosphamide in inducing remission of lupus nephritis and had a more favorable safety profile.

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The institutions and investigators participating in the study are listed in the Appendix.

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Intravenous cyclophosphamide has been the standard of care for treating severe lupus glomerulonephritis[1]; however, its use is limited by potentially severe toxic effects including bone marrow suppression, hemorrhagic cystitis, opportunistic infections, malignant diseases, and premature gonadal failure.[2] Clinical trials of treatment with intermittent intravenous cyclophosphamide combined with corticosteroids show greater long-term renal survival but not overall survival, as compared with treatment with corticosteroids alone.[3-6] Furthermore, failure to achieve remission, which is associated with an increased rate of progression to renal failure, is reported in 18 to 57 percent of patients who received cyclophosphamide.[7-10]

Mycophenolate mofetil, an immunosuppressive agent approved for the prevention of transplant rejection, has been used in patients with lupus nephritis that is refractory to cyclophosphamide and in patients who cannot tolerate cyclophosphamide.[11-14] Pilot studies of mycophenolate mofetil were uncontrolled and often appeared to be biased toward a poor outcome, given patients' history of therapeutic failures.

In the present study, the efficacy, safety, and tolerability of oral mycophenolate mofetil plus corticosteroids were compared with those of intravenous cyclophosphamide plus corticosteroids for inducing remission of active lupus nephritis in an open-label, randomized, noninferiority study designed to include crossover to the alternative regimen among patients who did not have an early response to the study therapy.

METHODS

STUDY DESIGN

We conducted a multicenter, randomized, open-label, controlled trial from December 1999 (when the first patient enrolled underwent randomization) through October 2003 (completion of the study). Eligibility criteria included systemic lupus erythematosus meeting four classification criteria of the American College of Rheumatology[15]; renal biopsy documenting lupus nephritis according to the classification of the World Health Organization as proliferative glomerulonephritis class III (focal), IV (diffuse), or V (membranous); and clinical activity as defined by one or more of the following: incident decrease in renal function (serum creatinine, >1.0 mg per deciliter [88.4 μmol per liter]), proteinuria (defined as more than 500 mg of protein in a 24-hour urine specimen), microscopic hematuria (defined as >5 red cells per high power-field) or the presence of cellular casts, increasing proteinuria with rising levels of serum creatinine, active urine sediment (hematuria or cellular casts), or serologic abnormality (anti-DNA antibodies or hypocomplementemia). To ensure that patients whose biopsy specimens indicated less severe disease required immunosuppressive therapy, those with class III or V lupus nephritis were required to have a serum creatinine level greater than 1.0 mg per deciliter or proteinuria greater than 2 g in a 24-hour urine specimen. Exclusion criteria were creatinine clearance of less than 30 ml per minute, serum creatinine on repeated testing greater than 3.0 mg per deciliter (265.2 μmol per liter), severe coexisting conditions precluding immunosuppressive therapy or conditions requiring intravenous antibiotic therapy, prior treatment with mycophenolate mofetil, treatment with intravenous cyclophosphamide within the past 12 months, monoclonal antibody therapy within the past 30 days, or pregnancy or lactation.

Institutional review boards at each study center approved the study design. Because therapeutic responses may differ depending on the pattern of renal histologic features, the patients were stratified according to renal biopsy as having proliferative glomerulonephritis (class III or IV), as compared with membranous glomerulonephritis (class V). Permuted blocks of patients of variable size (two through six) were used within each group. Treatment was assigned at a central site with the use of sealed envelopes. All patients gave written, informed consent before undergoing randomization.

TREATMENT PROTOCOL

Mycophenolate mofetil was initiated at a dose of 500 mg twice daily, and the dose was increased to 750 mg twice daily at week 2 and advanced weekly to a maximum dose of 1000 mg three times daily unless the white-cell count fell below 3000 per cubic millimeter. Intravenous cyclophosphamide was given as monthly pulses according to a protocol of the National Institutes of Health (NIH).[3] Dosage was modified on the basis of the nadir white-cell count of 2500 cells or less per square meter of body-surface area at 7 to 10 days after the infusion. Patients received prednisone at a dose of 1 mg per kilogram of body weight per day, with tapering by 10 to 20 percent at one-week or two-week intervals, on the basis of clinical improvement. The new appearance

or worsening of manifestations of extrarenal disease could be treated with one three-day pulse of intravenous methylprednisolone or increased doses of corticosteroids to a maximum of 2 mg per kilogram per day. Standard laboratory assessments were performed locally at entry into the study and at monthly intervals, to assess the efficacy and toxic effects of the study drugs.

STUDY END POINTS

The primary end point was complete remission at 24 weeks, defined as the return to within 10 percent of normal values of serum creatinine levels, proteinuria, and urine sediment. A secondary end point was partial remission at 24 weeks, defined as improvement of 50 percent in all abnormal renal measurements, without worsening (within 10 percent) of any measurement. Additional secondary end points included changes in renal function, complement components, anti–double-stranded DNA (dsDNA) antibody titers, and serum albumin levels.

As a safety measure, assessment of the therapeutic efficacy of the treatment after 12 weeks identified patients who did not have an early response, defined as an improvement of 30 percent in at least two measures of renal function (serum creatinine, proteinuria, or urine sediment) if all three measures were abnormal at entry into the study, or an improvement of 30 percent in one measure if one or two others were abnormal, provided no measures that were normal at baseline became abnormal. Treatment failure was defined as a condition requiring higher doses of corticosteroids for disease control, failure to meet the criteria for an early response, or failure to reach complete or partial remission at 24 weeks. Toxic effects requiring discontinuation of the study drug or withdrawal from the study for any other reason was also considered treatment failure.

STATISTICAL ANALYSIS

The protocol was designed as a noninferiority trial[16] to demonstrate that mycophenolate mofetil is at least as efficacious as intravenous cyclophosphamide as induction therapy for active lupus nephritis. The criterion for establishing noninferiority was that the lower bound of the two-sided 95 percent confidence interval for the difference in rates of complete remission (mycophenolate mofetil minus intravenous cyclophosphamide) must exceed the predefined noninferiority margin (minus 10 percent). To determine the size of the sample, we assumed a rate of expected complete remission at 24 weeks in the cyclophosphamide group of 30 percent. On the basis of anecdotal success with mycophenolate mofetil in cyclophosphamide-resistant nephritis, the likelihood that mycophenolate mofetil would be even more efficacious as primary therapy, and the drug's low reported incidence of serious toxic effects,[11,12] the rate of complete remission with mycophenolate mofetil was expected to be between 40 and 45 percent. Under these assumptions, a sample size of 70 patients in each of the two treatment groups was calculated to yield 80 percent power to conclude that mycophenolate mofetil was not inferior to intravenous cyclophosphamide with a one-sided alpha level of 0.025.

The analysis was based on the intention-to-treat principle, regardless of treatment adherence. The proportions of patients in the two groups who had complete remission and partial remission at 24 weeks were compared with the use of Pearson's chi-square test. In our primary analysis, patients for whom outcome data were missing because of loss to follow-up were assumed not to have had a response. The data were also analyzed by including only patients for whom outcome information was available. Differences in the baseline characteristics between the two groups and changes from baseline at each time point were evaluated with the use of the two-sample t-test for continuous variables and the chi-square test for categorical variables. Times to event for the end points of partial and complete remission were analyzed with the use of the Cox proportional-hazards model. All reported P values are two-sided. No interim analyses were performed.

The study was designed as a 24-week induction trial with no protocol specified for maintenance therapy. Data were not collected prospectively with regard to post-induction outcomes or therapy. Subsequently, the study sites were asked to provide laboratory data, data on maintenance therapy, and dates of nephritis flares, renal failure, and death at years 1 and 2 after randomization and at the last follow-up visit with the use of a standard database.

This investigator-generated study was designed and conducted by the authors (with other site investigators), and the data were analyzed solely by the authors, who hold the data and prepared the manuscript. Roche Laboratories provided a supplemental grant but had no role in the design and conduct of the study or in the analysis of the results.

RESULTS

Of 140 patients recruited at 19 study sites, 71 were assigned to mycophenolate mofetil and 69 to intravenous cyclophosphamide. The characteristics of the patients in the two groups were similar at baseline (Table 1).

STUDY END POINTS

At 12 weeks, 56 patients in the mycophenolate group and 42 in the cyclophosphamide group had responses that met the criteria for an early response (Fig. 1). Seven patients (9.9 percent) assigned to mycophenolate mofetil and 15 patients (21.7 percent) assigned to cyclophosphamide were lost to

Table 1. Characteristics of Patients at the Beginning of Induction Therapy.*

Characteristic	Mycophenolate Mofetil (N=71)	Intravenous Cyclophosphamide (N=69)	P Value†
Age — yr	32.5±10.0	31.0±9.0	0.35
Female sex — no. (%)	61 (86)	65 (94)	0.10
Duration of SLE — mo	43.7±66.9	58.7±80.6	
Race or ethnic group — no. (%)‡			0.38
Black	43 (61)	36 (52)	0.32
White	12 (17)	12 (17)	0.94
Hispanic	10 (14)	18 (26)	0.08
Asian	6 (8)	2 (3)	0.16
Other		1	
Renal biopsy according to WHO class — no. (%)§			0.99
III	11 (15)	11 (16)	0.94
IV	39 (55)	37 (54)	0.88
V	14 (20)	13 (19)	0.90
Mixed membranoproliferative	7 (10)	8 (12)	0.74
Serum creatinine — mg/dl¶	1.06±0.52	1.08±0.49	0.84
Urine protein — g per 24-hr urine sample	4.1±3.1	4.4±3.5	0.54
Nephrotic-range proteinurea — no. (%)‖	30 (42)	32 (46)	0.62
Serum albumin — g/dl	2.81±0.95	2.69±0.56	0.36
Serum C3 — mg/dl**	69.6±30.0	71.9±31.5	0.67
Serum C4 — mg/dl**	13.2±8.5	15.7±14.7	0.22
dsDNA antibodies††	1.26±1.05	1.29±1.0	0.85
Urinalysis			
White cells — per HPF	12.6±23.5	10.3±17.3	0.51
Red cells — per HPF	24.1±50.3	33.2±115.5	0.56
Cellular casts — no. (%)‡‡	13 (18)	10 (14)	0.54
Prior intravenous cyclophosphamide — no. (%)	6 (8)	7 (10)	0.73

* Plus–minus values are means ±SD. WHO denotes World Health Organization, anti-dsDNA anti–double-stranded DNA antibodies, SLE systemic lupus erythematosus, and HPF high-power field.
† P values were calculated with the use of Student's t-test for continuous variables and with the use of the chi-square test and Fisher's exact test for categorical variables.
‡ Race was self-determined.
§ Because of rounding, percentages may not total 100.
¶ To convert values for creatinine to micromoles per liter, multiply by 88.4.
‖ Nephrotic-range proteinurea was defined as 3.5 g of protein per 24-hour urine sample.
** Because the normal ranges for serum complement C3 and C4 assayed at the study sites varied, values were corrected to a single normal reference range for each (for C3, 83 to 201 mg per deciliter, and for C4, 16 to 47 mg per deciliter).
†† Because values for anti-dsDNA antibodies obtained at local study sites varied owing to the use of different methods of measurement, the values were converted into scores based on the degree of abnormality as determined at each site, with normal given a score of 0, mild abnormality 1, moderate abnormality 2, and severe abnormality 3.
‡‡ On urinalysis, samples containing any cellular casts (granular, red, or white cells) were recorded as positive.

follow-up. In the intention-to-treat analysis, assuming that those lost to follow-up did not have an early response, 16 of 71 patients in the mycophenolate group (22.5 percent) and 4 of the 69 patients in the intravenous cyclophosphamide group (5.8 percent) had complete remission, yielding an absolute treatment difference of 16.7 percentage points (95 percent confidence interval, 5.6 to 27.9 percentage points; P=0.005). Since the lower bound of the confidence interval not only exceeds the predetermined noninferiority margin (minus 10 percent) but also exceeds 0 percent, both the noninferiority and the superiority of mycophenolate mofetil to intravenous cyclophosphamide are demonstrated. When patients for whom outcome data were missing were excluded from the analysis, 16 patients (25.0 percent) of 64 in the mycophenolate group had complete responses, and 4 patients (7.4 percent) of 54 in the cyclophosphamide group had complete responses, a difference of 17.6 percent (95 percent confidence interval, 4.9 to 30.3 percent; P=0.01).

Partial remission occurred in 21 patients (29.6 percent) in the mycophenolate mofetil group and 17 patients (24.6 percent) in the cyclophosphamide group in the intention-to-treat analysis (P=0.51). When these totals are combined, 37 patients (52.1 percent) of the 71 assigned to mycophenolate mofetil and 21 patients (30.4 percent) of the 69 assigned to cyclophosphamide had either complete or partial remission (P=0.009). Similar results were

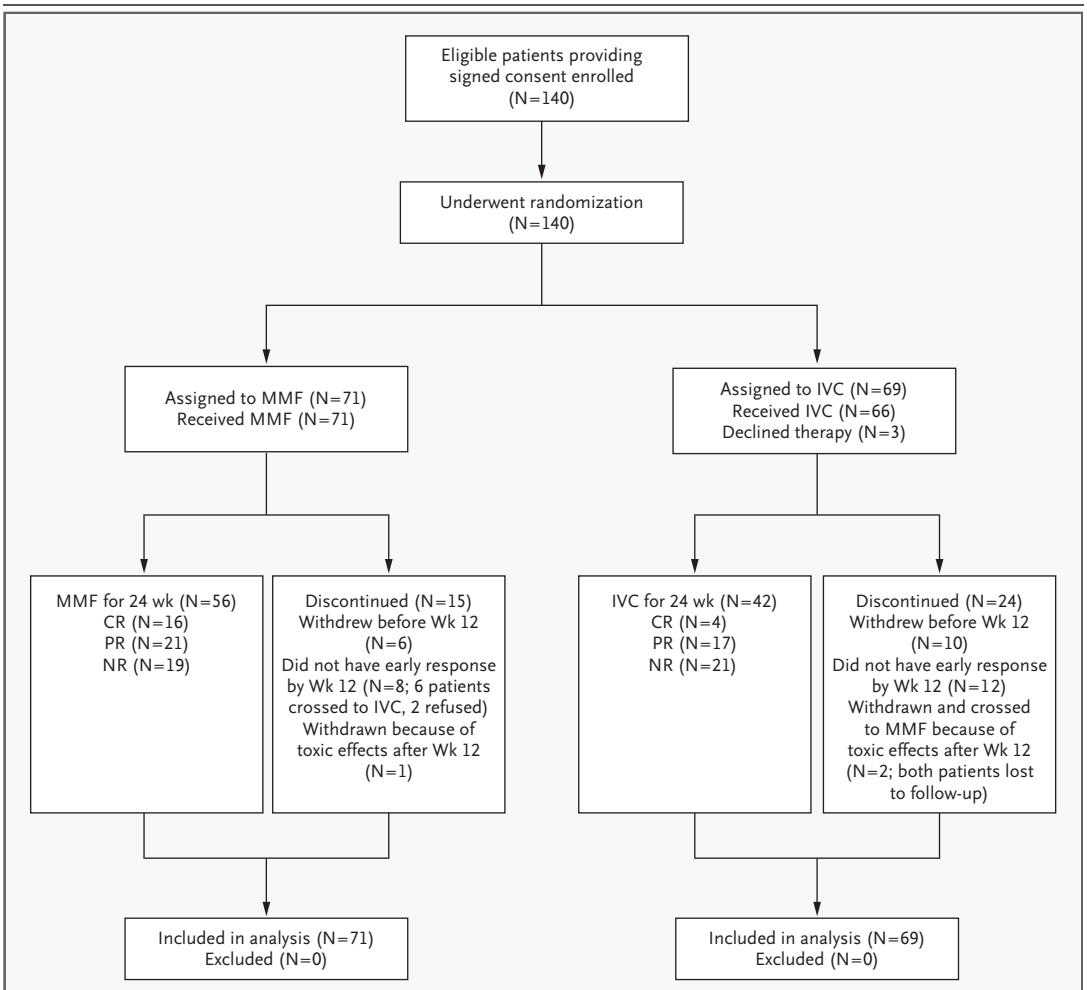

Figure 1. Enrollment of Patients, Treatment Assignments, and Outcomes, According to the Intention-to-Treat Analysis.
MMF denotes mycophenolate mofetil, IVC intravenous cyclophosphamide, CR complete response, PR partial response, and NR no response.

obtained after patients lost to follow-up were excluded from the analysis.

Patients in whom treatment failed included all those without complete or partial remission at 24 weeks, plus those who stopped treatment for any reason, yielding failure rates of 34 of 71 (47.9 percent) in the mycophenolate mofetil group, as compared with 48 of 69 in the cyclophosphamide group (69.6 percent, P=0.01) (Fig. 1). At 24 weeks, the differences between the two groups with respect to levels of serum creatinine, proteinuria, urine sediment (red and white cells), serum albumin, complement C3 and C4, and anti-dsDNA were not significant (Table 2).

RATES OF CROSSOVER AND WITHDRAWAL

Twenty-four patients were withdrawn from the study, 9 in the mycophenolate mofetil group and 15 in the cyclophosphamide group (Fig. 1). Of the nine in the mycophenolate mofetil group, five were withdrawn within 3 to 60 days after randomization because of the increasing severity of disease. One of these patients was withdrawn because of noncompliance with the protocol; two of the eight patients who did not have an early response refused to change therapy to cyclophosphamide; and one withdrew because of a generalized rash. Of the 15 patients in the cyclophosphamide group who withdrew, 3 patients refused treatment; 3 patients were withdrawn because of the severity of disease, 6 were withdrawn because of noncompliance, and 1 was withdrawn because lymphopenia developed. Two patients in this group were lost to follow-up.

IMMUNOSUPPRESSIVE THERAPY

The mean maximal tolerated dose of mycophenolate mofetil was 2680 mg per day; of a total of 83 patients receiving mycophenolate mofetil (including those who crossed over to the therapy), 52 (63 percent) tolerated a dose of 3000 mg per day. Of the 69 patients in the intravenous cyclophosphamide group, 43 (62 percent) received six monthly doses of the drug. The cumulative dose of cyclophosphamide per patient after three months was 3430±355 mg, and after six months it was 7302±1695 mg.

The mean dose of cyclophosphamide among

Table 2. Laboratory Values for Primary and Secondary End Points.*

Variable	12 Weeks of Treatment				24 Weeks of Treatment			
	MMF	IVC	Difference (95% CI)	P Value†	MMF	IVC	Difference (95% CI)	P Value†
Serum creatinine — mg/dl‡	0.96±0.36	0.98±0.68	0.02 (−0.17 to 0.21)	0.84	0.91±0.25	0.85±0.28	0.06 (−0.5 to 0.17)	0.27
Albumin — g/dl	3.26±0.29	3.17±0.25	0.09 (−0.01 to 0.19)	0.07	3.42±0.42	3.44±0.25	0.02 (−0.12 to 0.16)	0.79
Urine protein — g/24 hr	2.50±3.01	2.97±3.06	0.47 (−0.60 to 1.54)	0.39	2.03±2.79	1.46±1.27	0.57 (−0.35 to 1.49)	0.22
Urinalysis								
White cells per HPF	5.65±18.28	4.59±9.50	1.06 (−4.23 to 6.36)	0.69	2.89±4.60	10.51±41.19	7.62 (−3.38 to 18.62)	0.17
Red cells per HPF	12.53±19.28	20.22±94.39	7.69 (−16.02 to 31.40)	0.52	5.80±9.03	13.90±64.17	8.10 (−9.11 to 25.31)	0.35
Cellular casts — no. (%)§	6/63 (9.52)	5/53 (9.43)	0.09	0.99	6/49 (12.24)	3/40 (7.50)	4.74	0.46
C3 — mg/dl¶	101.41±22.78	87.80±35.79	13.61 (3.06 to 24.15)	0.01	96.84±29.93	91.87±29.52	4.97 (−7.18 to 17.12)	0.42
C4 —mg/dl¶	21.48±9.76	18.37±8.41	3.11 (0.20 to 6.42)	0.07	21.08±10.84	17.30±9.02	3.78 (−0.35 to 7.91)	0.07
Anti-dsDNA‖	0.66±0.82	0.82±0.68	0.16 (−0.11 to 0.43)	0.25	0.93±1.03	0.88±0.86	0.05 (−0.34 to 0.44)	0.80

* Plus–minus values are means ±SD. MMF denotes mycophenolate mofetil, IVC intravenous cyclophosphamide, CI confidence interval, HPF high-power field, and anti-dsDNA anti–double-stranded DNA.
† Student's t-test was used to determine P values for continuous variables, and the chi-square test was used to determine P values for categorical variables.
‡ To convert values for creatinine to micromoles per liter, multiply by 88.4.
§ A urinalysis showing any cellular casts (granular, red, or white cells) was recorded as positive.
¶ Because normal ranges for complement C3 and C4 assayed at participating sites varied, the values were corrected to a single normal reference range for each (83–201 mg per deciliter for C3, and 16–47 mg per deciliter for C4).
‖ Because values for anti-dsDNA antibodies obtained at local study sites varied according to the method used, values were converted to scores based on the degree of abnormality as determined at each laboratory, with a score of 0 assigned to normal values, 1 to mild abnormality, 2 to moderate abnormality, and 3 to severe abnormality.

patients receiving treatment for 24 weeks was 909.7±176.0 mg per square meter of body-surface area per month among those who had a complete response, 746.0±174.4 mg among those who had a partial response, and 725.5±190.3 mg among those who had no response. The use of prednisone therapy was similar in the two groups; patients in the mycophenolate mofetil group received mean doses of prednisone at baseline, week 12, and week 24 of 47.8±19.0 mg per day, 24.1±16.4 mg, and 12.9±11.0 mg, respectively. In comparison, patients in the cyclophosphamide group received mean doses at these time points of 49.5±20.2 mg per day, 23.5±15.4 mg, and 14.1±11.6 mg, respectively (P=0.67, P=0.81, and P=0.60, respectively).

ADVERSE EVENTS

There were two deaths in the cyclophosphamide group during treatment. One patient died from a cerebral hemorrhage within a week of receiving the first dose. The other patient received two doses, the second of which was delayed by sepsis; death occurred three weeks later and was related to active lupus and recurrent sepsis. A third patient assigned to cyclophosphamide declined therapy and died from pulmonary hemorrhage and renal failure at another hospital. There were no deaths during treatment in the mycophenolate mofetil group.

Infection and gastrointestinal side effects accounted for most of the adverse events (Table 3). Severe infections (pneumonia and lung abscess, necrotizing fasciitis, and gram-negative sepsis) occurred only with intravenous cyclophosphamide. Pyogenic infections were significantly less frequent among patients receiving mycophenolate mofetil than among those receiving cyclophosphamide (relative risk, 0.36; P=0.030). Hospitalizations for vomiting and dehydration occurred in five patients (a total of seven episodes) receiving cyclophosphamide. Diarrhea occurred more frequently with mycophenolate mofetil (15 patients) than with cyclophosphamide (2 patients); 3 patients in the mycophenolate mofetil group had chronic diarrhea, 1 of whom required a reduction in the dose to 1750 mg per day.

Apparent drug-related hematologic toxic effects were uncommon. Incident neutropenia alone was responsible for a reduction in the dose of cyclophosphamide at only eight infusions among six patients. Baseline lymphopenia was present in 22 patients in the mycophenolate mofetil group and 15 patients in the cyclophosphamide group; in 13 patients and 2 patients, respectively, the lymphopenia was resolved. Herpes simplex developed in four patients with lymphopenia in the cyclophosphamide group and in two patients with lymphopenia in the mycophenolate mofetil group, both of them within one week of entry into the study. One patient treated with mycophenolate mofetil had an exten-

Table 3. Adverse Events.*

	Mycophenolate Mofetil (N=83)	Intravenous Cyclophosphamide (N=75)
Severe infections†	1	6
Necrotizing fasciitis	0	1
Gram-negative sepsis	0	1
Pneumonia, lung abscess	1	4
Other infections	3	5
Oral or vaginal candida	4	8
Tinea of skin, nails	1	5
Cellulitis, skin abscess	5	7
Herpes zoster	3	4
Mucocutaneous herpes	1	4
Varicella	0	1
URI, bronchitis, pharyngitis	18	18
Urinary tract infection	5	4
Upper GI symptoms (nausea, vomiting, bloating, epigastric pain)	23	25
Chronic or recurrent episodes	4	10
Diarrhea	15	2
Persistent	3	0
Rectal bleeding	0	3
Lymphopenia (new onset)‡	18	28
Sustained lymphopenia	5	14
Neutropenia§	1	1
Anemia unrelated to SLE	2	2
Menstrual irregularities	8	11
Change in menstrual cycle	8	13
Amenorrhea	0	2
Alopecia unrelated to SLE	0	8
Severe generalized rash	1	0
Urticaria or angioedema	1	0
Duration of therapy (patient-wk)	1738	1350

* The patients in each of the two groups include those initially assigned to the regimen and those who crossed over to the regimen. Adverse events during crossover therapy are included. URI denotes upper respiratory infection, GI gastrointestinal, and SLE systemic lupus erythematosus.
† Severe infections were defined as those requiring intravenous antibiotic therapy.
‡ Lymphopenia was defined as fewer than 800 lymphocytes per cubic millimeter.
§ Neutropenia was defined as fewer than 1000 neutrophils per cubic millimeter.

sive rash that recurred with rechallenge. Menstrual irregularities occurred in 8 patients receiving mycophenolate mofetil, as compared with 11 patients receiving cyclophosphamide, 2 of whom had irreversible amenorrhea.

After induction therapy, the subsequent risks of renal flare, renal failure, and death on the basis of the initial induction-treatment assignment were examined with the use of a survival analysis of data collected after completion of the study protocol (Table 4). Although data on laboratory values and maintenance therapy after induction were not always available for individual patients, the duration of follow-up was similar in the two groups (36.2±16.9 months in the mycophenolate mofetil group vs. 37.2±16.9 months in the intravenous cyclophosphamide group, P=0.72). Renal failure and death were twice as frequent among patients in the cyclophosphamide group, as compared with those in the mycophenolate mofetil group, but the number of events was small and was not statistically significant.

DISCUSSION

Despite the general acceptance of cyclophosphamide as the standard of care in lupus nephritis, serious toxic effects and imperfect efficacy have led to the search for alternative treatments. On the basis of anecdotal reports of success with mycophenolate mofetil in patients with lupus nephritis at high risk for poor outcomes, we hypothesized that mycophenolate mofetil would have an efficacy equivalent to that of intravenous cyclophosphamide in inducing remission of active nephritis, with fewer toxic effects and better acceptance by patients.

Before our trial was completed, two randomized studies comparing mycophenolate mofetil with cyclophosphamide for lupus nephritis were reported. Chan et al. reported on a 12-month study involving 42 patients with class IV nephritis in which mycophenolate mofetil was as effective as oral cyclophosphamide in inducing remission. In their study, the rate of infectious complications was similar in the two treatment groups, but only patients treated with cyclophosphamide had amenorrhea, alopecia, or leucopenia, or died.[17] Hu et al. reported on 46 patients with class IV nephritis and concluded that six months of mycophenolate mofetil was more effective than intravenous cyclophosphamide in reducing proteinuria, hematuria, and autoantibody production.[18]

In our short-term study, the toxicity and tolerability profile of mycophenolate mofetil compared favorably with that of cyclophosphamide. Although upper gastrointestinal symptoms were common in the two groups, in the mycophenolate mofetil group the symptoms tended to be mild and self-limited, whereas in the intravenous cyclophosphamide group dehydration following treatment necessitated seven hospitalizations. Our findings are consistent with those in other studies; Mok and Lai noted that gastrointestinal intolerance was the most common side effect of mycophenolate mofetil but rarely led to withdrawal of the drug.[19] The good tolerance among our patients may have been due to the regimen of gradual dose increases. Serious infections were less common with mycophenolate mofetil, which was similar to the findings of Hu et al.[18] and of Chan et al.[17]

Our prospective controlled study was relatively large and involved a heterogeneous cohort, including patients from 19 academic and private-practice centers in the United States. Fifty-six percent of the patients were black, a subgroup often underrepresented in clinical trials but constituting a majority among Americans with lupus. Race was self-determined. Black race, minority ethnic background, and low socioeconomic status are associated with poor outcome — an outcome not mitigated by cyclophosphamide therapy.[20-24] Therapeutic success in our study, in which high-risk patients were the majority, may be related to the high target dose of 3 g per day of mycophenolate mofetil. This regimen was based on transplantation data suggesting that black patients require higher doses of this agent.[25,26]

A limitation of our study is that treatment assignment was not blinded. Although this could lead

Table 4. Outcomes during Follow-up after Induction Therapy.*

Event	No. of Events		Relative Risk (95% CI)†	P Value
	Mycophenolate Mofetil	Intravenous Cyclophosphamide		
First renal flare	8	8	0.98 (0.37–2.61)	0.96
Renal failure	4	7	0.53 (0.15–1.81)	0.31
Death	4	8	0.48 (0.15–1.60)	0.24

* Relative risks were determined with the use of the Cox proportional-hazards model.
† Values are for mycophenolate mofetil therapy as compared with intravenous cyclophosphamide therapy.

to potential bias in patient recruitment and in the interpretation of results, the marked differences in the side-effect profiles of the two drugs would probably make true blinding difficult. Potential bias was minimized by selecting a primary end point with the use of objective laboratory measures. Although the early crossover design was chosen for safety, it may have led to a premature designation of treatment failure. In recent reports, the average time to remission with cyclophosphamide is 10 months.[9,27] Our low response rate with cyclophosphamide may reflect an inability to achieve the recommended NIH protocol dosing; doses were regulated on the basis of toxic effects, primarily gastrointestinal symptoms. The trend toward better response with higher doses of cyclophosphamide highlights the association between efficacy and tolerability.

Another limitation of our study is its short duration and the restriction to induction therapy. Long-term experience in clinical trials using intravenous cyclophosphamide shows a relapse rate of up to 45 percent in patients with proliferative lupus nephritis, despite a complete clinical response to induction therapy.[28] Furthermore, the type of maintenance therapy after successful intravenous cyclophosphamide appears to be important; Contreras et al. found the composite end point of death or chronic renal failure and the rate of relapse-free survival to be significantly higher with mycophenolate mofetil than with cyclophosphamide.[29] Hospitalizations, amenorrhea, infections, and upper gastrointestinal symptoms were also significantly less frequent with mycophenolate mofetil than with cyclophosphamide. In contrast to the study by Contreras et al., an interim report by Chan et al. suggested an increased rate of flare associated with low-dose mycophenolate mofetil maintenance, as compared with azathioprine.[30] The long-term follow-up (median, 63 months) in the study by Chan et al. showed a similar rate of renal relapse in both treatment groups with more gradual tapering of the maintenance dose of mycophenolate mofetil[31] than in their initial study.[17]

Alternatives to cyclophosphamide and mycophenolate mofetil have been proposed, in particular maintenance with azathioprine.[29,32] Cost–benefit considerations are important. Despite the higher cost of mycophenolate mofetil, as compared with intravenous cyclophosphamide, there are additional costs associated with cyclophosphamide infusion, including reimbursement for the infusion unit and the cost for antiemetic agents, mesna, and leuprolide. Thus, the actual cost of cyclophosphamide therapy may surpass that of mycophenolate mofetil.

In summary, induction therapy with mycophenolate mofetil was superior to intravenous cyclophosphamide in inducing complete remission of lupus nephritis in this study. Mycophenolate mofetil appeared to be better tolerated than cyclophosphamide. Unresolved issues include determining the flare rate after induction with mycophenolate mofetil, as compared with that for cyclophosphamide, and determining the appropriate dose and duration of mycophenolate mofetil maintenance therapy.

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APPENDIX

The following institutions and investigators enrolled patients in the study: SUNY Downstate Medical Center, Brooklyn, N.Y. — E. Ginzler, C. Aranow; Hospital for Joint Diseases at NYU Medical Center, New York — J. Buyon; University of North Carolina at Chapel Hill, Chapel Hill — M. Dooley; St. Luke's–Roosevelt Hospital, New York — J. Merrill; Oklahoma Medical Research Foundation, Oklahoma City — J. Merrill; Johns Hopkins University, Baltimore — M. Petri; Cedars–Sinai Medical Center, Los Angeles — D. Wallace, M. Weisman; Columbia University, New York — G. Appel, J. Radhakrishnan; Medical University of South Carolina, Charleston — G. Gilkeson; George Washington

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