

Combination Therapy with Pulse Cyclophosphamide plus Pulse Methylprednisolone Improves Long-Term Renal Outcome without Adding Toxicity in Patients with Lupus Nephritis

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Background: Controlled trials in lupus nephritis have demonstrated that cyclophosphamide therapy is superior to corticosteroid therapy alone. The long-term effectiveness and side-effect profiles of pulse immunosuppressive regimens warrant further study.

Objective: To define the long-term risk and benefit of monthly treatment with boluses of methylprednisolone, cyclophosphamide, or both.

Design: Extended follow-up (median, 11 years) of a randomized, controlled trial.

Setting: U.S. government research hospital.

Patients: 82 patients with proliferative lupus nephritis.

Measurements: Rates of treatment failure (defined as need for supplemental immunosuppressive therapy or doubling of serum creatinine concentration, or death) and adverse events.

Results: In an intention-to-treat survival analysis, the likelihood

of treatment failure was significantly lower in the cyclophosphamide ($P = 0.04$) and combination therapy ($P = 0.002$) groups than in the methylprednisolone group. Combination therapy and cyclophosphamide therapy alone did not differ statistically in terms of effectiveness or adverse events. Of patients who completed the protocol ($n = 65$), the proportion of patients who had doubling of serum creatinine concentration was significantly lower in the combination group than in the cyclophosphamide group (relative risk, 0.095 [95% CI, 0.01 to 0.842]).

Conclusion: With extended follow-up, pulse cyclophosphamide continued to show superior efficacy over pulse methylprednisolone alone for treatment of lupus nephritis. The combination of pulse cyclophosphamide and methylprednisolone appears to provide additional benefit over pulse cyclophosphamide alone and does not confer additional risk for adverse events.

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Proliferative lupus nephritis is characteristically a protracted disease with a waxing and waning course (1, 2). Open-label and controlled clinical trials have shown that cyclophosphamide is superior to corticosteroids in preserving renal function; only a minority of patients treated with cyclophosphamide reach end-stage renal disease (3–14). Some retrospective analyses, however, have reported a less favorable effect of pulse cyclophosphamide therapy (15–17).

Lupus nephritis can reactivate after an initial response, and the cumulative renal damage may cause subsequent decline in renal function (18–20). Moreover, immunosuppressive therapy can be associated with adverse effects that are not evident during short-term clinical trials (21). Such complications must be weighed against morbidity from uncontrolled disease and the need for extended therapy. Long-term follow-up is therefore essential to assess the risk–benefit ratio of various immunosuppressive therapies.

Because immunosuppressive treatment regimens have dramatically reduced the frequency of end-stage renal disease, alternative outcomes to end-stage renal disease are needed as practical end points in clinical studies. In the analysis of a previous randomized, controlled trial (3), we used the composite outcome of “renal response” as the primary outcome. In that analysis, treatment with pulse cyclophosphamide, alone or in combination with pulse methylprednisolone, was superior to pulse methylprednisolone alone in inducing renal responses. In the same trial, combination therapy resulted in a higher rate of renal responses and fewer relapses compared with cyclophosphamide alone; however, these differences were not statistically significant after a median follow-up of 5 years (3). We report the results of extended follow-up and long-term effectiveness of these treatment regimens, as well as morbidity and mortality, in patients participating in this trial.

METHODS

Patients

Treatment during Protocol

Details of the treatment protocol have been published elsewhere (3). In brief, 82 patients with proliferative lupus nephritis were enrolled in a randomized, controlled study at the Clinical Center of the National Institutes of Health, Bethesda, Maryland, between 1986 and 1990. Initial analysis was based on data collected through 1 May 1995 (3). Patients were randomly assigned to receive one of three regimens: 1) intravenous methylprednisolone, 1 g/m² of body surface area, administered as a monthly bolus for at least 12 months and up to 36 months; 2) intravenous cyclophosphamide, targeting 1 g/m² of body surface area, as a monthly bolus for 6 consecutive months and then once every 3 months for at least 24 additional months; or 3) the combination of these two regimens. After the first year of the study, patients in any treatment group who were no longer receiving monthly therapy but had evidence of active glomerular disease were recycled to their originally assigned regimens. Recycling could not take place more than twice; if therapy failed three times, patients were considered nonresponders.

All patients initially received oral prednisone, 0.5 mg/kg of body weight daily, for 4 weeks. The prednisone dose was then tapered by 5 mg every other day each week to the minimal dose required to control extrarenal disease or to 0.25 mg/kg every other day, whichever was greater. For severe extrarenal flares of lupus, patients were permitted to receive prednisone, 1.0 mg/kg, daily for 2 weeks.

Post-Protocol Treatment

After completion of protocol treatment, therapy was dictated by clinical need and was determined by the patients' primary rheumatologist or nephrologist after consultation with the investigators at the National Institutes of Health.

Follow-up

We conducted a systematic follow-up of all patients through August 1999. The study was done under a protocol examining the natural history of systemic lupus erythematosus that was approved by the institutional review board of National Institute of Arthritis and Musculoskeletal and Skin Diseases and National Institute of

Diabetes and Digestive and Kidney Diseases, National Institutes of Health. All surviving patients were contacted and asked to return for evaluation. Patients who were unable or unwilling to return were asked to complete a standardized questionnaire about their renal status, current therapy, immunosuppressive therapy since the end of the protocol, and comorbid conditions. A copy of their medical records was also obtained with their permission. Family and physicians of deceased patients were contacted to collect data on the cause of death.

Patients evaluated at the National Institutes of Health underwent a detailed history and physical examination; laboratory studies; cardiac work-up (electrocardiography and echocardiography); bone densitometry (if not performed within 1 year of the follow-up visit) and magnetic resonance imaging of both hips unless they had a history of hip replacement or previous magnetic resonance imaging showing avascular necrosis. Data collection focused on determining renal outcomes (defined as persistent increase in serum creatinine concentration by at least 50%, persistent doubling of serum creatinine concentration, or end-stage renal disease) and illnesses associated with lupus nephritis or its treatment.

Definitions

Patients

Patients who completed the protocol ("protocol completers") were classified as responders or nonresponders on the basis of prespecified criteria. Protocol noncompleters were patients who underwent randomization but whose response to therapy could not be evaluated because they died before reaching an end point, did not return for follow-up, or were excluded because of protocol violation.

Renal Outcomes

"Renal response" was defined as an erythrocyte count less than 10 cells per high-power field in a centrifuged 50-mL urine sample, absence of cellular casts, and proteinuria less than 1 g/d. Response criteria were applied to protocol completers at the 5-year study visit. Patients were classified as nonresponders if they did not fulfill the above criteria for response at their 5-year visit or had received additional immunosuppressive therapy for worsening lupus nephritis beyond that allowed in the protocol before the end of 5-year follow-up.

Renal insufficiency was analyzed according to two grades of decreased renal function: increase in serum creatinine concentration to 50% or more or 100% or more (doubling) above the lowest concentration observed for at least 1 month during the protocol. End-stage renal disease was defined as receipt of renal replacement therapy (dialysis or kidney transplantation). Treatment failure was defined as the composite of any of the following events: need for immunosuppressive therapy not dictated by the protocol, doubling of serum creatinine concentration (compared with the lowest concentration during protocol treatment), or death.

Nonrenal Outcomes

Avascular necrosis of the bone was ascertained by performing screening magnetic resonance imaging of the hips. Ovarian failure was defined as sustained amenorrhea occurring before 45 years of age. Osteoporosis was defined according to the guidelines of the American College of Rheumatology (22). Ischemic heart disease was defined as history of myocardial infarction or coronary revascularization procedure or typical angina with a positive result on a stress test or ischemic changes on electrocardiography. Valvular heart disease was defined as a significant valvular abnormality on echocardiography, such as valvular thickening associated with vegetation, regurgitation, or stenosis. Hypertension was defined as sustained systolic blood pressure of 140 mm Hg or greater, sustained diastolic blood pressure of 90 mm Hg or greater, or receipt of antihypertensive medications. Hyperlipidemia was defined as a low-density lipoprotein cholesterol level greater than 3.36 mmol/L (130 mg/dL) or receipt of a cholesterol-lowering agent. "Serious infection" was any infection requiring intravenous antibiotics or hospitalization.

Statistical Analysis

For categorical outcome measures, we calculated the relative risk and 95% CIs. Survival data were plotted by using the Kaplan–Meier method, and the significance of differences between groups was tested by using the Breslow–Gehan–Wilcoxon test. We used an intention-to-treat approach to compare the effectiveness of the three treatments. For this analysis, we included all 82 enrolled patients and analyzed them as being in the treatment group to which they were assigned, regardless of the actual duration of treatment. A composite out-

come was used to assess treatment failure, in which therapy was considered to have failed at the earliest time at which patients required additional immunosuppressive therapy, had a doubled serum creatinine concentration, or died. Additional immunosuppressive therapy was defined as any immunosuppressive therapy not specified in the protocol, given for any reason and at any time after enrollment in the study. For example, if someone assigned to the methylprednisolone group was classified as a nonresponder after 3 years of therapy and was treated with cyclophosphamide, he or she would be classified as having had an event in the intention-to-treat survival analysis. Similarly, if a patient assigned to the cyclophosphamide group was still an active participant at the end of the protocol and continued to receive cyclophosphamide, he or she would be considered as someone who received additional immunosuppressive therapy and thus reached the composite end point (had an event). If a patient finished the protocol period as a responder but had a flare requiring immunosuppressive therapy after the protocol, he or she would be considered as someone with an event at that point. Protocol noncompleters were treated in the same manner. If a patient was withdrawn from the protocol—for example, because of pregnancy—and required immunosuppressive therapy after her pregnancy, she would be considered to have had an event at that time. Patients were censored only if they were lost to follow-up.

Relative risks and 95% CIs were calculated by using the SAS statistical software package (SAS Institute, Inc., Cary, North Carolina). All other statistical calculations were made by using StatView statistical software, version 5.0 (SAS Institute, Inc.). All *P* values were two tailed.

Role of the Funding Source

The study was funded by the intramural programs of the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

RESULTS

Extended Follow-up of All Patients

Patient Characteristics

Eighty-two patients were enrolled in the original protocol. Baseline characteristics in the three treatment groups were similar (3) (Table 1). Most patients were

Table 1. Patient Characteristics at Study Entry*

Characteristic	Cyclophosphamide Therapy (n = 27)		Combination Therapy (n = 28)		Methylprednisolone Therapy (n = 27)	
	Protocol Noncompleters (n = 6)	Protocol Completers (n = 21)	Protocol Noncompleters (n = 8)	Protocol Completers (n = 20)	Protocol Noncompleters (n = 3)	Protocol Completers (n = 24)
Median age at study entry, y	26	30	25	32	19	29
Women, n (%)	5 (83)	16 (76)	7 (87)	18 (90)	2 (66)	20 (83)
Ethnicity, n (%)						
White	5 (83)	12 (57)	5 (62)	13 (65)	3 (100)	18 (75)
African American	0 (0)	7 (33)	2 (25)	5 (25)	0 (0)	5 (20)
Other	1 (16)	2 (10)	1 (13)	2 (10)	0 (0)	1 (5)
Duration of lupus nephritis at study entry, mo	15.5 ± 7.6	26.6 ± 8.6	15.6 ± 6.6	48.3 ± 18.5	33.3 ± 20.1	30.7 ± 9.4
Activity index score	11.6 ± 1.0	8.9 ± 0.7	7.9 ± 1.4	8.4 ± 0.8	12.0 ± 2.8	7.8 ± 0.7
Chronicity index score	4.6 ± 1.1	2.6 ± 0.4	3.2 ± 0.8	2.8 ± 0.5	4.0 ± 1.2	2.5 ± 0.3
Renal biopsy results, n†						
WHO type III disease	0	6	2	4	0	6
WHO type IV disease	6	14	6	14	3	18

* Values with the plus/minus symbol are the mean ± SE. WHO = World Health Organization.

† Three patients did not have renal biopsy because of thrombocytopenia, anticoagulant therapy, or poorly controlled hypertension.

female (83%), were white (68%) or African-American (23%), and had World Health Organization class IV proliferative lupus nephritis (74%). The groups did not differ significantly in renal histology variables (activity and chronicity indexes).

Sixty-five patients completed the protocol and were classified as responders or nonresponders at 5 years; 17 patients were protocol noncompleters (Table 1). Reasons for noncompletion included pregnancy ($n = 2$), nonadherence ($n = 6$), protocol violation ($n = 5$), allergy to methylprednisolone ($n = 1$), and death ($n = 3$). Follow-up data were obtained on all 65 patients who completed the protocol. Data on renal outcome and mortality were available for 15 of 17 censored patients. Two of 17 censored patients were lost to follow-up because they failed to return for treatment during the protocol.

Additional Immunosuppressive Therapy

Thirty-four patients required additional immunosuppressive therapy after the protocol. Treatments consisted of high-dose corticosteroids ($n = 2$), pulse cyclophosphamide ($n = 26$), or both agents ($n = 6$). Eighteen of these 34 patients were originally assigned to the methylprednisolone group, 10 were assigned to the cyclophosphamide group, and 6 were assigned to the combination therapy group. Reasons for additional therapy included continuous renal disease activity ($n = 24$), renal flare ($n = 9$), or major extrarenal flare ($n = 1$).

Mortality and Renal Morbidity

At the end of extended follow-up (median, 11 years), 20 patients (8 in the cyclophosphamide group, 4 in the combination therapy group, and 8 in the methylprednisolone group) had doubling of serum creatinine concentration. Of these patients, 15 progressed to end-stage renal disease (5 in the cyclophosphamide group, 4 in the combination group, and 6 in the methylprednisolone group). The apparent equality in renal outcomes between the cyclophosphamide and methylprednisolone groups is probably related to the high rate of secondary cyclophosphamide treatment among patients initially assigned to the methylprednisolone group: ultimately, 17 of 27 (63%) patients in the methylprednisolone group received cyclophosphamide.

Eleven of the 82 patients died since enrollment in the study (Table 2). The two deaths from infection were probably related to pulse therapy.

Treatment Effectiveness

Breslow–Gehan–Wilcoxon analysis showed no difference among the three treatment groups in risk for death or end-stage renal disease in an intention-to-treat analysis (data not shown). To further evaluate treatment effectiveness and to capture all important aspects of treatment failure, we used the composite end point of death, progression of renal disease (defined as doubling of serum creatinine concentration), or need for additional immunosuppressive therapy not specified in the

protocol. All 82 patients were included, regardless of the duration of therapy or whether they completed the protocol. In this analysis (Figure), patients receiving cyclophosphamide or combination therapy were significantly less likely than those receiving methylprednisolone to experience treatment failure. Although the cyclophosphamide and combination therapy groups did not differ statistically in this analysis, fewer patients in the combination group than in the cyclophosphamide group reached the composite end point (8 of 28 [28%] vs. 13 of 27 [48%]) (relative risk, 0.59 [95% CI, 0.29 to 1.2]).

Adverse Events and Comorbid Conditions

We determined the frequency of selected comorbid conditions in patients with lupus nephritis and analyzed the occurrence of adverse effects associated with cyclophosphamide and methylprednisolone therapy (Table 2).

Fourteen patients (6 in the methylprednisolone group, 5 in the combination therapy group, and 3 in the cyclophosphamide group) developed avascular necrosis of the bone during the treatment protocol. At the end of the extended follow-up, 21 patients had avascular necro-

sis, with no overall difference among the three groups; avascular necrosis was symptomatic in 16 patients, of whom 9 required surgery (4 in the methylprednisolone group, 4 in the combination therapy group, and 1 in the cyclophosphamide group). The difference between the cyclophosphamide group and the other two groups was not statistically significant (relative risk, 0.72 [CI, 0.27 to 1.94] for symptomatic avascular necrosis and 0.26 [CI, 0.03 to 1.91] for avascular necrosis requiring surgery); however, the observed rate of avascular necrosis requiring surgery in the cyclophosphamide group was lower than in the other two groups. The estimate of risk is very imprecise because of the small sample and low event rate, and it may not be possible to statistically discern substantive proportional differences in risk. The prevalence of osteoporosis, another common side effect of corticosteroid therapy, was also similar in all three groups (Table 2).

Five patients had bacterial infections necessitating hospitalization after the end of the treatment protocol. Three of the five patients received cyclophosphamide at or within 6 months before infection (Table 2). The

Table 2. Rates of Morbidity, Comorbid Conditions, and Adverse Events at the End of Extended Follow-up in All Patients*

Event	Cyclophosphamide Therapy	Combination Therapy	Methylprednisolone Therapy
Avascular necrosis			
Total, n/n (%)	7/19 (36)	8/21 (31)	6/20 (30)
Symptomatic disease, n	4	6	6
Disease requiring surgery, n	1	4	4
Osteoporosis, n/n (%)	5/21 (23)	5/24 (21)	3/24 (13)
Premature amenorrhea, n/n (%)	12/20 (60)	12/23 (52)	7/21 (33)†
Median age at onset of premature amenorrhea, y	33	37	35
Infection, n/n (%)			
During the protocol‡	7/27 (26)	9/28 (32)	2/27 (8)
Major infection after the protocol	0/20 (0)	0/22 (0)	5/26 (19)§
Herpes zoster infection			
Total, n/n (%)	7/27 (26)	9/28 (32)	2/27 (7)
During the protocol, n/n	4/27	6/27	1/27
After the protocol, n/n	5/20	3/23	1/26
Death**	5/27	5/28	1/27

* Number of patients with a documented event over the number of patients for whom data were available.

† Five of 7 patients received cyclophosphamide after completion of methylprednisolone therapy.

‡ For details, see reference 3.

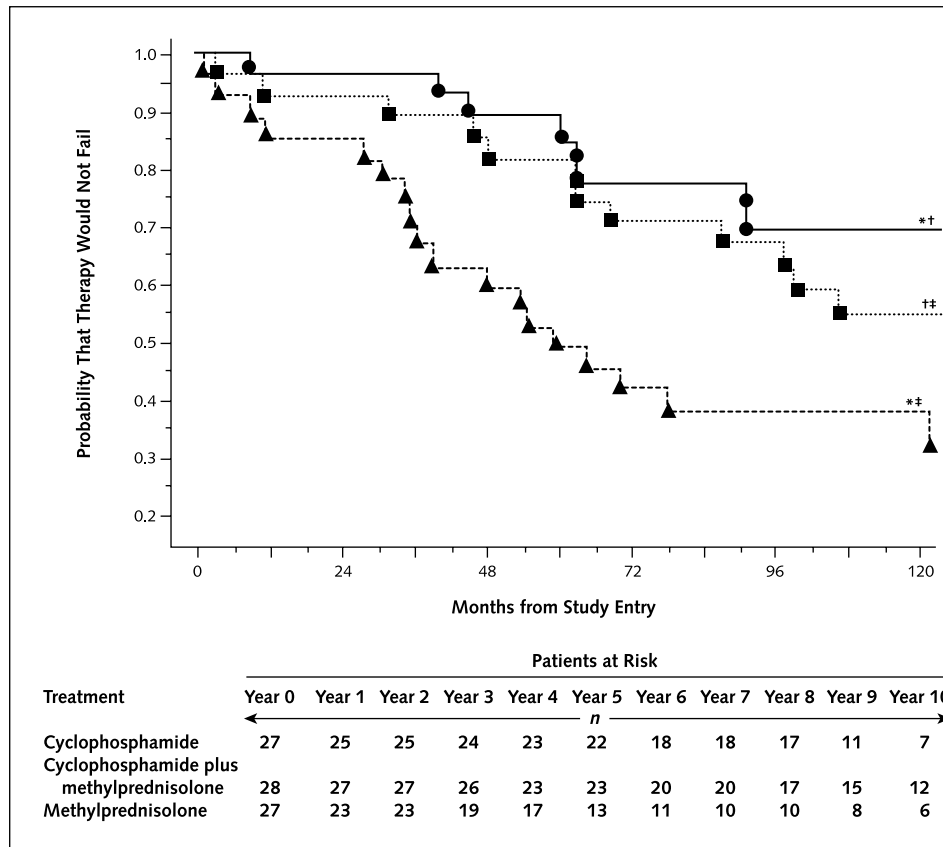
§ Three of 5 patients were receiving cyclophosphamide at or within 6 months before development of infection (acute bronchitis, atypical pneumonia, cellulitis, or bacterial sepsis). In 1 patient, peritonitis and sepsis was diagnosed more than 18 months after the last dose of cyclophosphamide. Two episodes of bacterial infections (sepsis and pneumonia) were seen in a patient who never received cyclophosphamide.

|| Cumulative number of patients with herpes zoster infection. Some patients had episodes of herpes infections both during and after the protocol.

¶ Relative risk, 3.93 (95% CI, 0.97 to 15.86) for cyclophosphamide-containing regimens versus methylprednisolone.

** Causes of deaths were as follows. Cyclophosphamide group: acute myocardial infarction, thrombotic thrombocytopenic purpura, retroperitoneal bleeding after kidney biopsy at another center, *Pneumocystis carinii* pneumonia, and cerebrovascular accident. Combination therapy group: acute myocardial infarction while receiving hemodialysis, postoperative complications, sepsis while receiving peritoneal dialysis, intracerebral hemorrhage, and AIDS. Methylprednisolone group: acute myelogenous leukemia (patient had never received alkylating agents).

Figure. Kaplan–Meier analysis of failure of therapy with cyclophosphamide plus methylprednisolone (circles), cyclophosphamide only (squares), or methylprednisolone only (triangles).



All patients entered in the study are included, regardless of length of therapy. Treatment failure was defined as death, doubling of serum creatinine concentration, or need for immunosuppressive therapy not specified in the protocol to control renal or extrarenal lupus activity, whichever occurred first. The Breslow–Gehan–Wilcoxon test was used for all comparisons. * $P = 0.002$ vs. methylprednisolone; † $P = 0.24$ vs. cyclophosphamide; ‡ $P = 0.04$ vs. methylprednisolone.

cumulative number of serious infections did not statistically differ among the three groups. Herpes zoster infections were more common in the cyclophosphamide and combination groups, primarily because of the higher number of infections during the treatment protocol (Table 2). The prevalence of hypertension, hyperlipidemia, and valvular heart disease did not differ among the three treatment groups at the end of extended follow-up (data not shown).

Follow-up of Protocol Noncompleters

Four patients who did not complete the protocol died (2 in the cyclophosphamide group and 2 in the combination group). Overall, renal outcome was significantly worse among noncompleters than completers. At

the time of withdrawal from the protocol, 6 patients fulfilled criteria for renal response: 2 of them subsequently progressed to end-stage renal disease and 1 died of cardiac arrest. Of the 9 patients who did not fulfill criteria for response at the time of withdrawal, 6 progressed to end-stage renal disease and 1 developed acute renal failure before she died of septic shock. Protocol noncompleters were relatively younger at study entry than completers, but noncompleters and completers did not differ significantly in ethnicity, sex, time from diagnosis of lupus nephritis, renal activity, or chronicity indices at baseline (Table 1). Of note, protocol noncompleters had a high rate of deteriorating renal function even though they received immunosuppressive therapy for at least 1 year after exiting the protocol.

Extended Follow-up of Completers

In contrast to noncompleters, only 6 patients (4 in the methylprednisolone group and 2 in the cyclophosphamide group) who completed the protocol reached end-stage renal disease. Eleven patients (5 in the cyclophosphamide group and 6 in the methylprednisolone group) had persistent doubling of serum creatinine concentration. Serum creatinine concentration persistently increased by more than 50% in 18 patients (8 in the cyclophosphamide group, 9 in the methylprednisolone group, and 1 in the combination therapy group) (Table 3).

At the end of the treatment protocol, most patients (4 of 5) who had doubled serum creatinine concentrations or reached end-stage renal disease were in the methylprednisolone group. During extended follow-up, 14 of 24 patients who completed the protocol in the methylprednisolone group subsequently received cyclophosphamide. This may account for the lack of apparent difference between the cyclophosphamide and methylprednisolone groups at the end of extended follow-up (Table 3). Because cyclophosphamide treatment of those patients may confound the long-term results, we restricted our subsequent comparison of long-term treatment effects to the cyclophosphamide and combination therapy groups only. No patient in the combination group progressed to end-stage renal disease or had doubling of serum creatinine concentration; in contrast, in the cyclophosphamide group, 3 patients had end-stage renal disease and 5 had doubled serum creatinine concentration. This finding suggests a benefit of combining cyclophosphamide and methylprednisolone. Compared with patients who received cyclophosphamide only, those who received combination therapy had a significantly lower rate of 50% increase in serum creatinine

concentration (1 of 20 vs. 8 of 21; relative risk, 0.16 [CI, 0.03 to 0.84]) and a clinically important decrease in the rate of doubled creatinine concentration (0 of 20 vs. 5 of 21; relative risk, 0.095 [CI, 0.011 to 0.842]).

Rates of adverse events were similar in the cyclophosphamide and combination therapy groups (Table 4). At the end of extended follow-up, the groups did not differ in the frequency of serious infections, premature amenorrhea, or corticosteroid-related adverse events (avascular necrosis, osteoporosis, and hyperlipidemia). Ischemic heart disease was diagnosed in four patients in the combination therapy group and one patient in the cyclophosphamide group; this difference, however, was not statistically significant.

DISCUSSION

Our long-term follow-up study (median, 11 years) demonstrated a persistent benefit of immunosuppressive regimens in patients with lupus nephritis. Of the 65 patients who completed the protocol, 54 (83%) had preserved renal function at the end of follow-up, with no clinically significant increase in their serum creatinine concentrations. Eleven protocol completers (17%) had doubled serum creatinine concentrations, including 6 (9%) patients who reached end-stage renal disease. None of the 20 protocol completers in the combination therapy group had doubling of serum creatinine concentration or reached end-stage renal disease compared to 5 and 2 of 21 patients, respectively, in the cyclophosphamide group. Rates of side effects and overall mortality did not differ significantly among the treatment groups. Nine of the 17 patients who did not complete the protocol progressed to end-stage renal disease.

To evaluate the long-term effectiveness of the dif-

Table 3. Renal Outcomes in Protocol Completers at the End of Extended Follow-up*

Outcome	Cyclophosphamide Therapy (n = 21)		Combination Therapy (n = 20)		Methylprednisolone Therapy (n = 24)†	
	End of Protocol	Follow-up	End of Protocol	Follow-up	End of Protocol	Follow-up
50% increase in creatinine concentration	2	8‡	2	1‡	5	9
Doubling of creatinine concentration	1	5§	0	0§	4	6
End-stage renal disease	1	2	0	0	3	4

* Some patients received additional immunosuppressive therapy after the protocol (see text for details). Data represent the renal status of protocol completers at the end of extended follow-up, regardless of post-protocol treatment.

† Fourteen of 24 patients received cyclophosphamide after they had completed the study.

‡ Relative risk, 0.16 (95% CI, 0.03 to 0.84) for combination therapy versus cyclophosphamide.

§ Relative risk, 0.095 (CI, 0.01 to 0.84) for combination therapy versus cyclophosphamide.

Table 4. Rates of Comorbid Conditions and Adverse Events at the End of Extended Follow-up in Protocol Completers*

Event	Cyclophosphamide Therapy (n = 21)	Combination Therapy (n = 20)
	<i>n/n</i>	
Hypertension	10/20	10/20
Ischemic heart disease	1/19†	4/19†
Hyperlipidemia	7/20	8/19
Valvular heart disease	9/19	7/21
Avascular necrosis‡	6/21	6/20
Osteoporosis	4/18	3/19
Premature menopause§	9/16	10/18
Major infections	7/21	9/20
Herpes zoster infection	6/21	5/20

* Number of patients with a documented event/number of patients for whom data were available.

† Not significant.

‡ Avascular necrosis was symptomatic in 1 patient receiving cyclophosphamide and 2 patients receiving combination therapy.

§ In women only.

ferent treatments, we applied an intention-to-treat approach by including all 82 patients in a Breslow–Gehan–Wilcoxon analysis that used a composite end point capturing all significant aspects of failure of therapy: need for additional treatment, doubling of serum creatinine concentration, or death. In this approach, both cyclophosphamide-containing regimens were superior to treatment with methylprednisolone alone. Patients assigned to the two cyclophosphamide-containing regimens had significantly higher rates of herpes zoster infection. The addition of pulse methylprednisolone to pulse cyclophosphamide, however, did not seem to increase the frequency of this complication. Of note, rates of adverse events frequently seen with corticosteroids, such as avascular necrosis of the bone and osteoporosis, did not seem to be higher when methylprednisolone was added to cyclophosphamide. On the other hand, use of methylprednisolone alone as initial therapy did not seem to result in lower rates of premature amenorrhea, a predictable complication of cyclophosphamide therapy (23). These data are encouraging; however, the size of the cohort and the lack of treatment regulation in the follow-up phase may have masked more subtle differences.

Patients who did not complete the protocol had worse long-term outcome than patients who completed the protocol, regardless of treatment assignment or whether they met criteria for response. The reasons for

this discrepancy are not immediately apparent. Comparison of baseline clinical and demographic characteristics did not reveal any consistent differences in the pattern of adverse prognostic factors between the two groups; however, our study may be underpowered to detect subtle baseline differences. Moreover, most noncompleters received at least 1 year of immunosuppressive treatment, and most were treated subsequently with cyclophosphamide. Inconsistent follow-up and delays in treatment because of nonadherence or other reasons, such as pregnancy, may account for adverse outcomes among noncompleters. These data emphasize the importance of vigilant surveillance and aggressive management of proliferative lupus nephritis.

During extended follow-up, therapy was not based on a predefined treatment protocol but rather on consensus of a group of rheumatologists and nephrologists with expertise in lupus nephritis. However, the long duration of follow-up (median, 11 years), the completeness of the follow-up (information was available on all but two patients), the consistent pattern of differences between the cyclophosphamide and combination groups both at the end of the protocol and at the end of extended follow-up, and the presence of data suggesting that addition of methylprednisolone to cyclophosphamide causes no added toxicity justify cautious confidence in the interpretation of these observations. Taken together, the data suggest that combination therapy is highly effective for treatment of proliferative lupus nephritis and should be considered the treatment of choice for patients with severe disease. Controlled studies have shown that plasmapheresis does not improve the clinical outcome in patients treated with prednisone and cyclophosphamide (24). Alternative therapies are needed for patients refractory to these agents. Mycophenolate mofetil (25, 26), high-dose cyclophosphamide without stem-cell transplantation (27), and bone marrow transplantation (28–32) have been evaluated in preliminary studies; larger controlled studies are under way. Biological agents, such as anti-CD40 ligand and CTLA4-Ig, are promising as therapies that interfere with specific steps of the pathogenesis of lupus and are being evaluated in clinical studies (33).

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