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Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis

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Pulse cyclophosphamide is more effective than prednisone alone in preventing renal failure in lupus nephritis. We undertook a randomised, controlled trial to find out whether pulse methylprednisolone could equal pulse cyclophosphamide in preserving renal function in patients with lupus nephritis, and whether there was a difference between long and short courses of pulse cyclophosphamide in preventing exacerbations.

65 patients (60 female, 5 male; median [range] age 29 [10–48] years) with severe lupus nephritis were assigned randomly to monthly pulse methylprednisolone for 6 months (25 patients), monthly pulse cyclophosphamide for 6 months (20), or monthly cyclophosphamide for 6 months followed by quarterly pulse cyclophosphamide for 2 additional years (20). Patients treated with pulse methylprednisolone had a higher probability of doubling serum creatinine than those treated with long-course cyclophosphamide ($p < 0.04$). Risk of doubling creatinine was not significantly different between short and long course cyclophosphamide. However, patients treated with short-course cyclophosphamide had a higher probability of exacerbations than those treated with long-course cyclophosphamide ($p < 0.01$).

An extended course of pulse cyclophosphamide is more effective than 6 months of pulse methylprednisolone in preserving renal function in patients with severe lupus nephritis. Addition of a quarterly maintenance regimen to monthly pulse cyclophosphamide reduces the rate of exacerbations.

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Introduction

Survival of patients with systemic lupus erythematosus (SLE) has improved greatly in recent years, but lupus nephritis remains an important cause of morbidity and mortality.[1] Immunosuppressive drugs are more efficacious than prednisone alone[2] in controlling clinical signs of active nephritis,[3] in preventing renal scarring,[4] and, ultimately, in reducing the risk of end-stage renal disease.[5,6] Among cytotoxic drug regimens, intermittent pulse

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cyclophosphamide appears to have one of the highest therapeutic indexes in renal[5-8] and major extra-renal complications of SLE.[8-10] There are, however, certain disadvantages to pulse cyclophosphamide—namely, complexity of administration, drug-induced nausea and vomiting, concern about long-term toxicity, and uncertainty about the optimal intensity and duration of treatment.

Uncontrolled trials have led to the widespread use of pulse methylprednisolone in management of lupus nephritis.[11-17] This practice is based primarily on apparent reduction in the rate of corticosteroid side-effects and possible increased efficacy compared with conventional prednisone. We sought to determine, first, whether pulse methylprednisolone and pulse cyclophosphamide had comparable efficacy in the long-term management of lupus nephritis, and, second, whether there were differences in the efficacy and toxicities of short and long courses of pulse cyclophosphamide.

Patients and methods

Patient selection

Patients entered this open, controlled trial between 1981 and 1986. All patients were followed until death or the cut-off date for this report of June, 1991. No patients were lost to follow-up. 65 subjects (60 female, 5 male; median age at study entry 29 [range 10–48] years) were recruited. They had a median duration of SLE of 33 (1–228) months and of recognised renal involvement of 11 (1–189) months. At study entry, patients had four or more criteria for SLE[18] and severe lupus nephritis. Severe lupus nephritis was defined by a nephritic urine sediment and impaired renal function with a creatinine clearance between 25 and 80 ml per min. If creatinine clearance was higher than 80 ml per min, the candidate had to have very active renal histology with crescents or necrosis in more than 25% of glomeruli. Renal biopsies were obtained during the 6 weeks before study entry and were evaluated by light and electron microscopy.[19] Classification of lupus nephritis and of activity and chronicity indices was done as described previously.[20] Patients were excluded from the study if they were pregnant or had: received cytotoxic drug therapy for more than 10 weeks at any time,[5] active infections, insulin-dependent diabetes, or previous malignancy.

Treatment

After establishment of study eligibility and obtaining written informed consent, patients were assigned randomly to one of three treatment groups (drawn from a set of masked cards): intravenous infusion of 1·0 g/m² methylprednisolone over 30 min, initially in three daily doses, followed by monthly single doses for 6 months (25 patients); single monthly doses for 6 months of cyclophosphamide (0·5–1·0 g/m²) given by intravenous infusion over 60 min (20 patients); or single monthly doses for 6 months of cyclophosphamide, according to the regimen described above, followed by single quarterly doses (0·5–1·0 g/m²) for a further 2 years (20 patients). Intravenous cyclophosphamide was followed by infusion of 2 l/m² 0·45% saline over 24 h and patients were encouraged to urinate frequently; antiemetics were used as necessary. Cyclophosphamide was adjusted to a maximum of 1·0 g/m² if leucocyte counts did not drop below 1500/μl at the nadir on days 10–14 after treatment. Details of administration of pulse therapy have been published elsewhere.[21]

All patients were treated with prednisone, starting at 0·5 mg/kg per day and continuing for 4 weeks; the drug was then tapered at a rate of 5 mg every other day to the minimum dose required for control of extra-renal disease (but not less than 0·25 mg/kg every other day). After the first 6 months of pulse therapy, patients in all treatment groups with evidence of increased activity of lupus nephritis (worsening urine sediment, proteinuria escalating to greater than 3·5 g per day, and/or more than 25% decline in creatinine clearance) were treated with prednisone 1·0 mg/kg every other day for 1 month with rapid taper back to previous baseline doses. Patients were evaluated at least every 3 months for the first 30 months and at least every 6 months thereafter.

TABLE I—CHARACTERISTICS OF PATIENTS AT STUDY ENTRY BY TREATMENT GROUP

Variable	Methyl-prednisolone	Short-course cyclo-phosphamide	Long-course cyclo-phosphamide
Sex (f/m)	24/1	17/3	19/1
Race (black/other)	11/14	7/13	10/10
Proteinuria (>3·5 g per day)	13	15	12
Mean (SE) age (yr)	31 (2)	30 (2)	28 (2)
Mean (SE) packed cell volume	29 (1)	30 (1)	30 (1)
Mean (SE) creatinine (μmol/l)	169 (19)	177 (18)	142 (16)
Mean (SE) albumin (g/l)	27 (1)	28 (2)	26 (1)
Mean (SE) cholesterol (μmol/l)	7·9 (0·6)	8·0 (0·6)	8·3 (0 5)
Mean (SE) complement, C3 (g/l)	0·73 (0·06)	0·72 (0·07)	0·75 (0·07)
Mean (SE) DNA binding (%)*	74 (9)	60 (8)	55 (10)
Mean (SE) proteinuria (g per day)	4·5 (0·6)	4 9 (0·7)	5·0 (0·8)

*Farr assay, normal <25% binding.

Follow-up and outcomes

The primary study outcome was renal insufficiency defined as sustained doubling (for more than 1 month) of serum creatinine over the lowest value reached during the study period. Patients were censored if they became pregnant (n=8: 1 receiving methylprednisolone, 3 on short-course and 4 on long-course cyclophosphamide), withdrew voluntarily (n=2: both on long-course cyclophosphamide), or required additional pulse therapy before meeting renal insufficiency outcomes (n=9: 1 on methylprednisolone, 6 on short-course and 2 on long-course cyclophosphamide). Of those patients requiring additional pulse cyclophosphamide, 1 on methylprednisolone and 1 on short-course cyclophosphamide were retreated because of persistently active nephritis; the remaining patients on short-course and both patients on long-course cyclophosphamide had an initially favourable response to therapy but were subsequently retreated because of relapses of active nephritis.

Exacerbations of lupus nephritis or severe systemic lupus were evaluated to define further the relative efficacy of short versus long courses of cyclophosphamide. Patients were considered at risk of exacerbation if they had shown (after study entry) a steady trend in improvement of urine sediment, proteinuria, renal function, and extra-renal disease activity in major organs. Exacerbations were defined as substantial worsening of two or more of these parameters, unresponsive to a month of increased prednisone as described above, such that reinstitution of pulse cyclophosphamide therapy was indicated.

TABLE II—RENAL HISTOLOGY AT STUDY ENTRY BY TREATMENT GROUP

Variable	Methyl-prednisolone	Short-course cyclo-phosphamide	Long-course cyclo-phosphamide
Number treated	25	20	20
Number biopsied	25	20	19
*Class of nephritis (no patients)**			
III (focal proliferative)	2	1	2
IV (diffuse proliferative)	22	17	17
V (membranous)†	1	2	0
Mean (SE) activity index	10 0 (0·9)	8·9 (1·0)	9·1 (0·8)
Mean (SE) chronicity index	3·6 (0·5)	4·4 (0 4)	3·7 (0·5)

*World Health Organisation classification system [19]
†Patients with predominantly membranous nephropathy also had a component of endocapillary proliferative disease

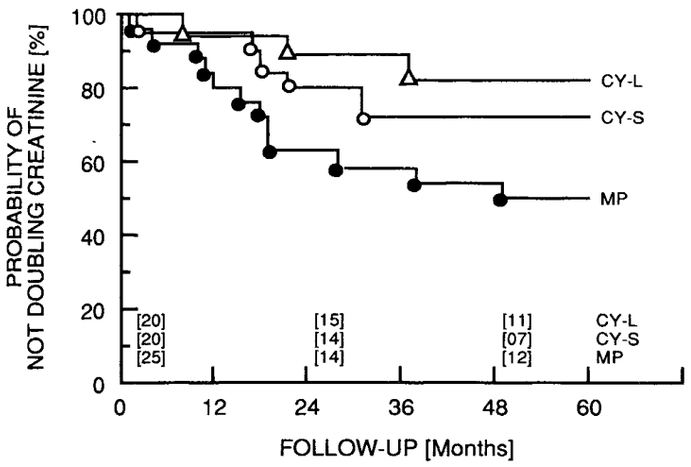

Fig 1—Cumulative probability of not doubling serum creatinine after treatment.

MP = methylprednisolone, CY-S = short-course pulse cyclophosphamide, CY-L = long-course pulse cyclophosphamide Numbers of patients at risk in each treatment group at various times are shown in parentheses along the abscissa Comparison of cumulative probabilities of renal insufficiency in the methylprednisolone and long-course cyclophosphamide groups shows a significant difference by the Gehan test (p = 0·037)

Statistical analysis

Considering that durations of patient follow-up were not uniform, cumulative survival analysis was used, with the time to renal insufficiency or to exacerbation as measures of outcome.[22] Equality of survival curves was assessed by the Gehan[23] test with BMDP statistical software.[24] Distribution of clinical and morphological attributes among treatment groups was examined by the Kruskal-Wallis and chi-square tests. Two-tailed tests were used to estimate p values.

Results

Patients tended to have more severe renal disease than reported in previous National Institutes of Health studies.[5,6] On study entry, 64% of patients had abnormal serum creatinine (≥114 μmol/l) and 62% had proteinuria indicating nephrosis (≥3·5 g per day). The distributions of demographic and laboratory features were not statistically different among the treatment groups (table I). Renal biopsy showed that most patients had diffuse proliferative lupus nephritis; 3 patients had mixed membranous and proliferative lupus nephritis (table II). Patients had high activity and chronicity indices, indicating a high probability of progressive renal failure.[25] The severity of lupus nephritis judged by clinical and pathological criteria was comparable in all treatment groups.

Renal outcomes are summarised in table III. In the methylprednisolone group, 48% had sustained doubling of serum creatinine, whereas this outcome occurred in 35% of the short-course cyclophosphamide group and in 15% of the long-course cyclophosphamide group.

The greatest risk of doubling serum creatinine was in patients receiving pulse methylprednisolone: after 3 years, the cumulative probability of doubling serum creatinine was over 40% (fig 1). Patients receiving an extended course of cyclophosphamide had the lowest cumulative probability of doubling serum creatinine—less than 10% after 3 years. Comparison of the probabilities of renal insufficiency in the methylprednisolone and long-course cyclophosphamide groups showed a significant difference by the Gehan test (p = 0·037). There were no significant differences in risk of doubling serum creatinine between the methylprednisolone and the short-course cyclophosphamide groups. We did not

TABLE III—RENAL OUTCOMES BY TREATMENT GROUPS*

Renal outcome	Methyl-prednisolone (n = 25)	Short-course cyclo-phosphamide (n = 20)	Long-course cyclo-phosphamide (n = 20)
Stable renal function	13 *(52)*	13 *(65)*	17 *(85)*
Doubled serum creatinine	12 *(48)*	7 *(35)*	3 *(15)*
End-stage renal disease	6 *(24)*	5 *(25)*	2 *(10)*

Figures are number of patients *(%)*
*Renal status was assigned at the time the patient met the renal outcome, was censored, or was last evaluated at study closure in June, 1991

analyse statistical differences in risk of end-stage renal failure among the treatment groups (table III) because, based on our previous results,[5,6] we could not justify withholding pulse cyclophosphamide from patients whose nephritis progressed beyond a doubling of serum creatinine.

Although the short course of pulse cyclophosphamide may be effective in reducing the risk of renal progression within the first few years and may be more tolerable and less toxic than extended therapy, the abbreviated treatment may not be optimal for preventing exacerbations of lupus nephritis. Thus, we evaluated possible differences between the short and long cyclophosphamide regimens in terms of the cumulative probabilities of exacerbation of major SLE activity. Patients were considered at risk for exacerbation only if they improved with pulse therapy, as described previously. Exacerbation was defined as SLE "flares" that warranted reinstitution of pulse therapy (after having failed to respond to temporary increases in alternate day prednisone). Risk of major exacerbation was analysed after completion of the intensive monthly phase of treatment, and after completion of all cyclophosphamide treatments.

After completion of the monthly phase of treatment, there was a significantly greater cumulative probability of exacerbations in patients on short-course cyclophosphamide than in those receiving long-course treatment (fig 2). Exacerbations in 9 of 11 patients that prompted reinstitution of pulse cyclophosphamide were due to worsening of active nephritis (declining renal function [9], increasingly active urine sediment [7], reappearance of nephrotic syndrome [3]). Exacerbations in 2 patients involved major extra-renal disease (central nervous system lupus [2], severe thrombocytopenia [1]).

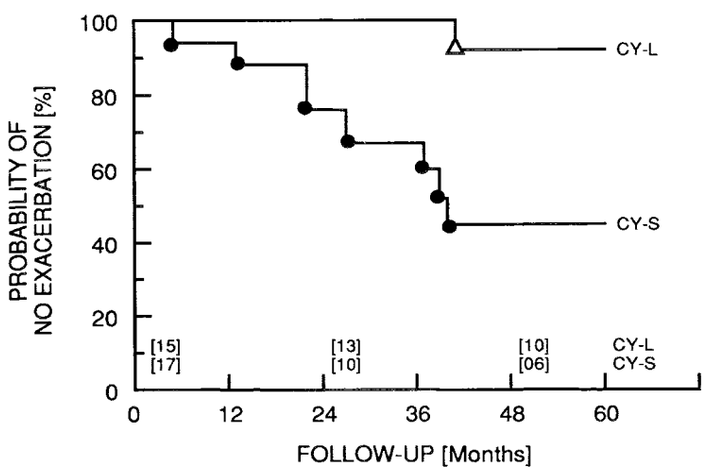

Fig 2—Cumulative probabilities of no exacerbation on completion of monthly cycles in groups receiving short (CY-S) or long (CY-L) courses of pulse cyclophosphamide.

Numbers of patients at risk in each treatment group are shown in parentheses along the abscissa Patients treated with long-course cyclophosphamide had significantly greater cumulative probability of no exacerbation than those treated with the short-course cyclophosphamide (Gehan test, p = 0·006)

TABLE IV—COMPLICATIONS ARISING IN EACH TREATMENT GROUP

Variable	Methyl-prednisolone	Short-course cyclo-phosphamide	Long-course cyclo-phosphamide
Major infection	0/25	*1/20	†1/20
Herpes zoster	3/25	2/20	1/20
Malignancy	0/25	0/20	‡1/20
Haemorrhagic cystitis	0/25	0/20	0/20
Premature ovarian failure§	0/15	3/16	5/13
Osteonecrosis‖	3/17	3/16	4/14
Cataracts	6/17	5/15	3/14

Figures are number observed/number at risk and evaluated for the specified complication
*Candida oesophagitis; †legionella pneumonia, ‡cervical carcinoma in situ, §patients at risk were women <45 years of age,[11] symptomatic bone disease documented by radiography, magnetic resonance imaging, or bone scan

The advantage of the long course of pulse cyclophosphamide appeared to be sustained after cyclophosphamide was completely finished. If risk of exacerbation is evaluated from the end of all pulse cyclophosphamide therapy (ie, after 6 months for short course and after 30 months for long course), risk remains lowest for the long-course cyclophosphamide group (data not shown). At the time of analysis, the difference in risk of exacerbation falls just short of significance ($p = 0{\cdot}09$). Statistical power was limited by the small number of patients at risk and by the shortened period of observation after completion of long-course cyclophosphamide. In summary, after short-course cyclophosphamide, rate of exacerbation was 13/1000 patient-months of observation; after long-course cyclophosphamide, the exacerbation rate was 2/1000 patient-months from the end of monthly therapy and 4/1000 patient-months from the end of quarterly pulse therapy.

Major infections and episodes of herpes zoster were rare and not related to any particular therapy (table IV). No episodes of haemorrhagic cystitis were observed. Not surprisingly, premature amenorrhoea was most frequent in the long-course cyclophosphamide group. We are continuing to analyse the rates of recovery of ovarian function in these patients. The only malignancy occurred in 1 patient in the long-course cyclophosphamide group who had carcinoma in situ of the cervix that was successfully treated with excision biopsy.

Discussion

Treatment of lupus nephritis has been the subject of controversy. In early controlled studies, treatment with cyclophosphamide was associated with greater probabilities of improvement and stability of renal parameters than treatment with corticosteroids alone.[3] However, these studies did not resolve the controversy about cyclophosphamide because there was no statistically significant reduction in the risk of end-stage renal failure within the first 5 years of observation. With longer follow-up, we observed a significant reduction in the risk of renal failure in patients receiving an extended course of cyclophosphamide compared with corticosteroids alone.[5,6] It was also evident that intermittent pulse cyclophosphamide was at least as efficacious as conventional oral cyclophosphamide, but pulse therapy had substantially reduced risks of serious complications. Accordingly, we have since tested only intermittent pulse regimens of cyclophosphamide.

Previous observations in a variety of immunological conditions, including SLE, suggested that pulse methylprednisolone gave increased efficacy and reduced rates of side-effects compared with conventional high-dose prednisone alone. Thus, in the present study, pulse methylprednisolone was chosen for comparison with pulse cyclophosphamide. Our choice of 6 months of treatment was arbitrary; at the time this study began, three daily doses of methylprednisolone followed by single monthly doses for 6 months was the most aggressive corticosteroid therapy that we were willing to administer. Most previous studies used only a short burst of pulse methylprednisolone for a few days at the start of therapy or for subsequent exacerbations of lupus nephritis. Only one study has evaluated monthly pulse methylprednisolone.[16]

The present study showed clearly that pulse methylprednisolone did not match the efficacy of a sustained course of pulse cyclophosphamide in preserving renal function in severe lupus nephritis. We did not formally evaluate the rate of exacerbation in patients treated with pulse methylprednisolone, because a high proportion exhibited renal progression and were switched to alternative therapies. A previous study[11] suggested that a high rate of exacerbation and/or persistent disease activity rendered short courses of pulse methylprednisolone a poor choice of therapy for severe lupus nephritis. On the other hand, uncontrolled studies seem to show that pulse methylprednisolone can be effective for patients with apparently milder forms of lupus nephritis.[26] Admittedly, the present study does not address all possible applications of pulse methylprednisolone in lupus nephritis. Studies are in progress to evaluate the efficacy and toxicity of longer and repeated courses of pulse methylprednisolone in severe lupus nephritis.

The optimal dose, treatment interval, and duration of pulse cyclophosphamide are not known; practices vary greatly.[5,8,27] The present study and our general clinical experience with lupus nephritis suggest that short courses of pulse cyclophosphamide are associated with higher rates of exacerbation than courses that include a period of "consolidation" therapy for several months after disease activity subsides. At present, we favour treatment with quarterly pulse cyclophosphamide for at least 1 year beyond the point where urinary sediment becomes inactive, proteinuria is less than 0·5 g per day, lupus serologies are normal (or at least stable), and extra-renal disease activity is quiet.

We thank Dr John L. Decker for his leadership during the planning and early implementation phases of this study. Dr Tatiana Antonovych and Dr Sharda Sabnis of the Nephropathology Section of the Armed Forces Institute of Pathology, Washington, DC, provided invaluable assistance in the evaluation of renal biopsies.

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Placebo-controlled trial of prednisolone in children intubated for croup

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Many studies have attempted to find out whether steroid treatment is beneficial in children with croup, but the results have been inconclusive. We have done a prospective placebo-controlled study of the effect of prednisolone on two clinical endpoints—the duration of intubation and the need for reintubation.

Reasons for exclusion were age under 6 months, congenital airway anomalies, and previous intubation. 70 eligible children were randomly assigned treatment with prednisolone 1 mg/kg (n=38) or placebo (n=32) every 12 h given by nasogastric tube until 24 h after extubation. 11 (34%) placebo-treated and only 2 (5%) prednisolone-treated patients required reintubation after accidental or elective extubation ($p=0.004$, Fisher's exact test; odds ratio 8·9, 95% confidence interval 1·7–59·3). Survival analysis with log-normal regression showed that the duration of intubation was shorter with steroid therapy ($p<0.003$) and increasing age ($p<0.02$), but was not influenced by endotracheal tube size or abnormality on chest radiograph. The median duration of intubation was 138 (95% CI 118–160) h in children who received placebo and 98 (85–113) h in the prednisolone group.

Steroid therapy reduces the duration of intubation and the need for reintubation in children intubated for croup.

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Introduction

Croup (acute laryngotracheobronchitis) is the commonest cause of acute upper airway obstruction in children. Steroid treatment is given to many children with croup in the hope that it will reduce airways obstruction caused by inflammation, but the efficacy is controversial. Many studies[1-12] have attempted to clarify the role of steroids in patients with croup before intubation, but there has been no prospective controlled trial of the use of steroids in children with croup after intubation. We have performed a prospective randomised double-blind comparison of prednisolone and placebo in children intubated for severe airways obstruction caused by croup.

Patients and methods

Patients were eligible for the trial if endotracheal intubation had been required for upper airway obstruction caused by croup. The diagnosis of croup was made on clinical criteria—coryzal symptoms, fever, barking cough, hoarse voice, inspiratory stridor, retraction, or cyanosis developing over several days.[13] We excluded children who were younger than 6 months old and those who had congenital airway anomalies, previous intubation, or spasmodic croup, defined as disease of sudden onset without preceding fever or symptoms of upper respiratory tract infection. A child was intubated if severe chest retractions developed or if he or she became exhausted despite treatment with nebulised adrenaline.

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