EXTENDED REPORT

EULAR randomised controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis

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Objective: To compare the efficacy and side effects of intermittent pulse cyclophosphamide plus methylprednisolone with continuous oral cyclophosphamide plus prednisolone, followed by azathioprine, in patients with proliferative glomerulonephritis caused by systemic lupus erythematosus (SLE).

Methods: A multicentre randomised controlled trial was conducted between June 1992 and May 1996 involving eight European centres. All patients satisfied the American College of Rheumatology criteria for SLE and had biopsy proven proliferative lupus nephritis. All received corticosteroids in addition to cytotoxic drugs, as defined in the protocol, for two years. The trial was terminated after four years as recruitment was disappointing.

Results: 32 SLE patients with lupus nephritis were recruited: 16 were randomised to intermittent pulse cyclophosphamide and 16 to continuous cyclophosphamide plus azathioprine. Mean duration of follow up was 3.7 years in the continuous group (range 0 to 5.6) and 3.3 years in the pulse group (range 0.25 to 6). Three patients were excluded from the pulse therapy group as they were later found to have pure mesangial glomerulonephritis. Two patients in the continuous therapy group developed end stage renal failure requiring dialysis, but none in the intermittent pulse therapy ($p = 0.488$; NS). There were similar numbers of side effects and withdrawals from treatment in both groups. There were three deaths: two in the intermittent pulse therapy group and one in the continuous therapy group.

Conclusions: There was no statistically significant difference in efficacy and side effects between the two regimens. Infectious complications occurred commonly, so careful monitoring is required during treatment.

The prognosis of systemic lupus erythematosus (SLE) has improved considerably over the last 40 years.[1] However, many studies have shown that lupus nephritis is associated with a poorer outcome.[2–4] Hence much interest has been generated in the use of cytotoxic drugs in the treatment of lupus nephritis, as high dose corticosteroids alone is often inadequate and is associated with unacceptable side effects. There have been relatively few controlled studies on the best treatment for lupus nephritis.

Cyclophosphamide has emerged as the mainstay of treatment to induce remission, following results from NIH studies that showed that intermittent pulse cyclophosphamide treatment was superior to azathioprine and steroids.[5–8] Unfortunately, there has been a division in opinion among physicians over whether it is best to give cyclophosphamide by intermittent pulse therapy or by continuous therapy.

This trial was designed to compare intermittent pulse cyclophosphamide and methylprednisolone with oral continuous cyclophosphamide and prednisolone for three months, followed by continuous azathioprine and prednisolone. The intermittent pulse cyclophosphamide protocol used in this trial was based on the Birmingham vasculitis protocol, but the drug dose was reduced by 33% and the interval between pulses increased owing to the frequent occurrence of cytopenias when the original vasculitis protocol was used in SLE patients.[9 10]

METHODS

Subjects and setting

An open label multicentre randomised controlled trial was conducted between June 1992 and May 1996 at eight European centres: Prague, Vienna, Vilnius, Leeds, Ljubljana, London, Lund, and Birmingham. Patients were eligible if they were aged 16 to 65 years, satisfied American College of Rheumatology criteria for SLE,[11] and had biopsy proven proliferative glomerulonephritis caused by SLE. The study was approved by the ethics committees at all participating centres, and signed consent was obtained from all patients before entry into the trial.

Renal biopsy was assessed locally at individual centres using standard WHO classification.[12] Patients were not eligible if they had had any cyclophosphamide or azathioprine treatment within the preceding three weeks, had pure membranous or pure mesangial proliferative glomerulonephritis on biopsy, previous treatment with cyclophosphamide for more than three months, allergy to the study drugs, previous malignancy, primary immunodeficiency (except complement components), or non-lupus-related renal disease.

The patients were stratified according to the presence of renal failure (defined as creatinine clearance less than 50 ml/min) and subsequently underwent block randomisation to either intermittent pulse therapy or continuous therapy. This trial was aimed to follow patients for five to 10 years;

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however, entry into the trial was terminated after four years as patient recruitment was disappointing and many patients had been withdrawn.

Intermittent pulse therapy protocol

Intermittent pulse cyclophosphamide therapy was given intravenously at a dose of 10 mg/kg three weekly for four doses, then orally at the same dose split over two days at four weekly interval for nine months, and finally at six weekly intervals for 12 months (appendix 1). Hence the total duration of treatment was two years. If the nadir neutrophil count at day 7 to 14 after the last pulse was greater than 4000/μl, the next dose of cyclophosphamide was increased by 25%. The maximum bolus dose of cyclophosphamide, regardless of weight, was 1000 mg. Dosage reductions were advised for cytopenias and renal impairment. If cytopenia (neutrophil count <2000/μl or platelet count <100 000/μl) occurred before bolus therapy after the last pulse, the bolus would be delayed until the cell counts were restored. If cytopenia recurred when the next pulse was due, the cyclophosphamide bolus was reduced by 25% unless there was bone marrow evidence that the cytopenia was caused by the SLE (rather than by previous cytotoxic therapy). In the presence of renal impairment, the cyclophosphamide dose was reduced to 7.5 mg/kg if serum creatinine was between 250 and 500 μmol/l (inclusive), and 5 mg/kg if serum creatinine was more than 500 μmol/l.

Pulse methylprednisolone was given intravenously at a dose of 6.6 mg/kg immediately before each intravenous pulse of cyclophosphamide and then orally at the same dose split over two days before each oral cyclophosphamide pulse (appendix 1). The maximum bolus dose of methylprednisolone, regardless of weight, was 1000 mg. No dosage modification was required for cytopenias or renal impairment.

Low dose daily oral prednisolone was given at an initial dose of 0.3 mg/kg/day to control non-renal lupus symptoms, reducing by 0.1 mg/kg/day with each pulse if possible to a maintenance dose of 0.05 mg/kg/day, or 0.1 mg/kg/day if necessary. Metoclopramide or ondansetron were recommended as antiemetics, and mesna was given orally as three doses, each at 25% of the cyclophosphamide dose in milligrams, at 0, 4, and 18 hours after cyclophosphamide, to prevent bladder toxicity.

Continuous therapy protocol

Daily oral cyclophosphamide was given at a dose of 2 mg/kg/day for three months. After three months, the oral cyclophosphamide was changed to daily oral azathioprine at a dose of 1.5 mg/kg/day. In the presence of renal impairment, the dose of cyclophosphamide was reduced to 1.75 mg/kg/day if the serum creatinine was between 250 and 500 μmol/l (inclusive) and to 1.5 mg/kg/day if the serum creatinine was more than 500 μmol/l. If a new cytopenia developed, cyclophosphamide or azathioprine was discontinued and a bone marrow biopsy was advised to assess whether this was caused by drugs or lupus. If lupus was responsible, treatment was resumed at the same dose. If therapy was responsible, it was restarted at 25% lower dose once the cell count was above the lower limits. Following the development of severe neutropenia in several patients on this regimen, the dose of oral cyclophosphamide was reduced to 1.5 mg/kg/day in September 1994.

Patients also received daily oral prednisolone starting at 0.85 mg/kg/day and reducing according to the protocol (appendix 2). The maximum daily dose of prednisolone was 60 mg.

Additional treatment

All patients were prescribed an H_2 receptor antagonist (ranitidine 150 mg at night or cimetidine 400 mg at night) and amphotericin lozenges (10 mg four times a day) as prophylaxis while on daily cyclophosphamide and for two weeks with each pulse of cyclophosphamide. Antihypertensive treatment would be given as necessary to keep diastolic blood pressure below 100 mm Hg.

If patients did not respond satisfactorily, and had increasing proteinuria or deteriorating renal function, additional immunosuppression could be given at any stage in the form of bolus intravenous methylprednisolone (1 g/day for three days), bolus intravenous cyclophosphamide (5 mg/kg/day for three days), or plasma exchange (six exchanges).

Assessments

All patients were assessed three monthly during the two year treatment period. Intercurrent diseases and treatments were recorded during each visit. Investigations that were undertaken before starting treatment, before each pulse therapy, and monthly during continuous therapy included full blood count, erythrocyte sedimentation rate, C reactive protein, serum creatinine, creatinine clearance, 24 hour urine for protein excretion, urine microscopy, urine culture, antinuclear antibody, anti-dsDNA antibody, C3 and C4. In addition, a full blood count was checked weekly in patients on three weekly pulse therapy and oral cyclophosphamide, and two weekly in those on four to six weekly pulse therapy. Patients on azathioprine had a full blood count checked two weekly for the first two months and four weekly thereafter.

End points

The primary end points were doubling of serum creatinine and renal failure requiring dialysis. Secondary end points were withdrawal from treatment, complications from treatment (infection, malignancy, haemorrhagic cystitis, amenorrhoea, alopecia, or nausea and vomiting), and death.

Statistical analysis

Based on the opinions of the investigators, it was estimated that 30% of patients treated with the oral continuous regimen would double their creatinine in 10 years. This study was designed to have the power of 80% to detect 20% difference in this outcome between the two regimens with an α error of 0.05 (two sided); hence it was calculated that 75 patients were required in each treatment arm, taking into account an estimated drop out of 20%.

Analysis was on an intention to treat basis using the χ^2 test or Fisher's exact test. A probability (p) value of less than 0.05 was considered statistically significant.

RESULTS

Thirty two patients were recruited, 26 of whom were female. Sixteen patients were randomised to pulse therapy and 16 to continuous therapy. Three patients were excluded from the pulse therapy group as they were mistakenly recruited, being later found to have pure mesangial glomerulonephritis on renal biopsy. The baseline characteristics of each group are shown in table 1. There was no significant difference in these characteristics between the two treatment groups. Duration of follow up was similar in both groups, with mean follow up of 3.7 years in the continuous group (range 0 to 5.6 years) and 3.3 years in the pulse group (range 0.25 to 6 years). Four patients were lost to follow up: two in the continuous therapy group and two in the pulse therapy group. The reasons were moving home away from the study centre, or the patient's decision not to continue with the study. None of the patients in either group required additional immunosuppressive treatment.

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Table 1 Baseline characteristics of the two treatment groups

Characteristic	Continuous	Pulse
Number of patients	16	13
Age (years) (mean (SD))	32.2 (11.7)	42.4 (11.8)
Female sex (%)	14 (87.5)	11 (84.6)
Race (%)		
White	5 (31.3)	4 (30.8)
Afro-Caribbean	1 (6.3)	0
Asian	0	1 (7.7)
Unknown	10 (62.5)	8 (61.5)
Raised creatinine (>120 μmol/l)	4 (25%)	5 (38.5%)
Renal histology (%)		
Class IV	10 (62.5)	8 (61.5)
Class III	6 (37.5)	5 (38.5)
Duration of renal disease (%)		
⩽1 year	10 (62.5)	10 (76.9)
2 years	4 (25)	0
3–6 years	2 (12.5)	3 (23.1)

Primary outcomes

Two patients (12.5%) in the continuous therapy group developed end stage renal failure requiring dialysis (table 2). One of them doubled the serum creatinine at two years of the treatment protocol and went on to dialysis more than three years after the start of treatment, while the other patient had required dialysis since the start of the study. In the pulse therapy group none of the patients doubled their creatinine or required dialysis. However, this difference was not statistically significant (Fisher's exact test, $p = 0.488$).

Secondary outcomes

There was no significant difference in withdrawal from therapy between the two treatment groups (table 2). There were more neutropenias in the continuous therapy group, and these were also more severe than in the pulse therapy group, but not all were associated with infections. There were similar numbers of infectious complications in both groups: in the continuous therapy group, two were viral, one viral plus bacterial, and one possibly fungal; in the pulse therapy group the infections were predominantly bacterial. There was more nausea and vomiting in the pulse therapy group, but this was predominantly in the oral part of the pulse regimen. There was one case of haemorrhagic cystitis in the continuous group but none in the pulse group. The only malignancy occurring in the study was a bronchial carcinoma in a 62 year old women in the pulse group who had been withdrawn three months into the study because of recurrent bronchopneumonia, possibly related to the tumour. Amenorrhoea occurred in one patient in each group and both of these patients were aged 40 years.

There were three deaths in the study—one in the continuous group with the other two in the pulse group. The only death in the continuous group occurred in a patient who had been withdrawn before starting the study drugs because of rapidly deteriorating renal function and infection. The cause of death in one patient in the pulse group was malignancy, while the other died late (3.3 years after the start of treatment) and the cause was not determined.

There was a similar number of withdrawals from treatment in both treatment groups (table 3), the majority because of adverse effects. In the pulse therapy group, infections were the main reason for withdrawal, while in the continuous group, neutropenia and infections were the most common reasons for withdrawal. Only one patient in each group had to be withdrawn because of failure to respond to the treatment protocol.

Table 2 Summary of outcomes in the pulse therapy (n = 13) and continuous therapy (n = 16)

Outcomes	Continuous therapy (%)	Pulse therapy (%)
Doubled serum creatinine	1 (6.3)	0
Dialysis	2 (12.5)	0
Neutropenia	3 (18.8)	1 (7.7)
Infections	4 (25)	5 (38.5)
Nausea/vomiting	1 (6.3)	3 (23.1)
Haemorrhagic cystitis	1 (6.3)	0
Malignancy	0	1 (7.7)
Permanent amenorrhoea	1 (6.3)	1 (7.7)
Withdrawn from therapy	7 (43.8)	7 (53.8)
Death	1 (6.3)	2 (15.4)

DISCUSSION

There has been a lack of studies directly comparing treatment with continuous oral cyclophosphamide and intermittent pulse cyclophosphamide. In the NIH study comparing different immunosuppressive regimens (including continuous oral cyclophosphamide and pulse cyclophosphamide), the results were obtained by comparing a few different regimens prescribed over different time periods.[5] Hence that study has to be interpreted with caution as it was not a properly controlled trial and the comparisons between different regimens were not direct.

Our present study was designed to address this issue. The pulse cyclophosphamide protocol used in this study was modified from the Birmingham vasculitis protocol, with shorter interval between pulses than in the NIH protocol. The rational for this was the rapid induction of disease remission, thereby reducing irreversible damage caused by the disease.

In our study, there was no statistically significant difference between intermittent pulse therapy and continuous therapy with regard to efficacy. Unfortunately, the study had inadequate power to detect a difference in efficacy between the two treatment regimens because recruitment proved harder than expected. Many physicians became reluctant to enter patients because of concerns that the oral regimen was slower to work and more toxic than the pulse regimen, following development of severe neutropenia in the continuous group. This led to the premature termination of the study.

There was a trend towards less severe adverse effects in the intermittent pulse regimen compared with the continuous oral regimen. Infections were common and occurred in about 30% of patients in both groups; hence there is a need for careful monitoring in all patients on cyclophosphamide treatment. There have been no cases of haemorrhagic cystitis in the pulse cyclophosphamide regimen, which is consistent with previous studies involving pulsed cyclophosphamide.[5–8] This is reassuring, as potential bladder toxicity on oral

Table 3 Reasons for withdrawal from treatment

Reason for withdrawal	Continuous therapy	Pulse therapy
Adverse effects	6 (37.5)	5 (38.5)
Failure to respond to treatment	1 (6.3)	1 (7.7)
Patient's choice	0	1 (7.7)

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cyclophosphamide is a major reason for physicians preferring pulsed cyclophosphamide to continuous cyclophosphamide.

The results of our study are similar to those of another study done in Hong Kong, which compared intermittent intravenous pulse cyclophosphamide with sequential oral cyclophosphamide followed by azathioprine.[13] However, it was not a randomised controlled trial, as the outcomes of one centre using pulse cyclophosphamide were compared with outcomes from another centre using sequential oral treatment. The dose of pulse cyclophosphamide used in that study was smaller, with longer intervals between pulses, than in the present study.

Although our study showed similar efficacy between the pulse and continuous regimens, one has to bear in mind that the duration of continuous oral cyclophosphamide was three months, which is much shorter than in previous studies with continuous cyclophosphamide. Longer courses of continuous cyclophosphamide may result in better efficacy, but this would be at the expense of more adverse effects—particularly haemorrhagic cystitis, which occurred in up to 17% of patients in previous studies.[5] In the NIH study comparing pulse intravenous cyclophosphamide and oral cyclophosphamide, a difference in renal outcome favouring pulse therapy only became apparent after five years.[5] Hence, the duration of follow up in out present trial may not be sufficient to show a difference between these two treatments.

In conclusion, this study shows that there is no great difference in efficacy between the oral continuous and intermittent pulse regimes for cyclophosphamide, but the initial dose of 2 mg/kg oral cyclophosphamide was felt by the investigators to be too toxic to persist with. The intermittent intravenous pulse regimen appears to be better tolerated than oral continuous treatment, with less severe adverse effects. We believe this effect would be more apparent if the oral pulse was replaced by intravenous pulse, as many patients in the pulse therapy group develop severe nausea and vomiting during the oral part of this regimen. It is therefore not surprising that the intermittent intravenous pulse regimen has been widely adopted as the mode of choice for cyclophosphamide administration in the treatment of lupus nephritis.[14 15]

Further studies with pulse cyclophosphamide are still required to define its role in the treatment of proliferative lupus nephritis. The efficacy and safety of shorter courses of pulse cyclophosphamide followed by other immunosuppressive agents such as azathioprine, cyclosporin A, and mycophenolate mofetil, need to be evaluated in clinical trials.

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APPENDIX 1

Intermittent pulse therapy protocol

Time (week)	Route	Cyclophosphamide dose	Prednisolone dose
0	iv	10 mg/kg×1	6.6 mg/kg×1
3	iv	10 mg/kg×1	6.6 mg/kg×1
6	iv	10 mg/kg×1	6.6 mg/kg×1
9	iv	10 mg/kg×1	6.6 mg/kg×1
12	oral	5 mg/kg×2	3.3 mg/kg×2
16	oral	5 mg/kg×2	3.3 mg/kg×2
20	oral	5 mg/kg×2	3.3 mg/kg×2
24	oral	5 mg/kg×2	3.3 mg/kg×2
28	oral	5 mg/kg×2	3.3 mg/kg×2
32	oral	5 mg/kg×2	3.3 mg/kg×2
36	oral	5 mg/kg×2	3.3 mg/kg×2
40	oral	5 mg/kg×2	3.3 mg/kg×2
44	oral	5 mg/kg×2	3.3 mg/kg×2
48	oral	5 mg/kg×2	3.3 mg/kg×2
52	oral	5 mg/kg×2	3.3 mg/kg×2
58	oral	5 mg/kg×2	3.3 mg/kg×2
64	oral	5 mg/kg×2	3.3 mg/kg×2
70	oral	5 mg/kg×2	3.3 mg/kg×2
76	oral	5 mg/kg×2	3.3 mg/kg×2
82	oral	5 mg/kg×2	3.3 mg/kg×2
88	oral	5 mg/kg×2	3.3 mg/kg×2
94	oral	5 mg/kg×2	3.3 mg/kg×2
100	oral	5 mg/kg×2	3.3 mg/kg×2
104	oral	5 mg/kg×2	3.3 mg/kg×2

iv, intravenous.

APPENDIX 2

Prednisolone dose in continuous therapy

Time from induction	Dose (mg/kg/d)
0–2 weeks	0.85
3–4 weeks	0.65
5–10 weeks	0.42
11–18 weeks	0.30
19–26 weeks	0.20
27–35 weeks	0.17
36–52 weeks	0.15
53–104 weeks	0.11

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