METHYLPREDNISOLONE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

39 patients who received pulse methylprednisolone for disease manifestations of systemic lupus erythematosus were studied for zero to twenty-four weeks following therapy. Pulse methylprednisolone was given as intravenous infusions of methylprednisolone (10 mg/kg body weight) over one hour each day for three consecutive days. 27 (69.2%) patients were treated for lupus nephritis, 12 (30.8%) patients for non-renal manifestations of lupus. 17 (63.0%) of the renal lupus patients and 7 (58.3%) of the non-renal lupus patients showed clinical response. 11 (28.2%) patients had infections from which 7 (63.6%) died. Overall, 15 (38.5%) patients died. Early deaths (occurring within the first two weeks) were mainly due to disease activity while later deaths were mainly due to infection. In conclusion, the majority of lupus patients appeared to have had a beneficial response to pulse methylprednisolone therapy.

Keywords: Renal lupus, Methylprednisolone, Non-renal lupus

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INTRODUCTION

Pulse methylprednisolone has gained wide acceptance as a mode of therapy for controlling renal and non-renal complications of systemic lupus erythematosus (SLE) (1-3). Its efficacy as an agent of disease control has been related to both the type of disease manifestation as well as the degree of reversibility of that manifestation. Reports of the success rate have been variable due to the heterogeneity of the patients that have been studied. Its main advantage has been cited as the rapid provision of high dose corticosteroid while limiting the incidence and severity of side-effects. The hazards that have been encountered in its use include cardiac arrythmias and arrest as well as hypotension. The purpose of this study was to evaluate the experience of this mode of therapy in patients with SLE in our department and to determine if it was of benefit in controlling disease complications of SLE.

METHODS

A retrospective review of 39 consecutive patient records during the years 1984 to 1987 was made.

The indications for pulse therapy, i.e. renal or non-renal were noted. Indications were deemed to be renal if pulse therapy was administered primarily to control complications of lupus nephritis. Pulse Methylprednisolone was administered as intravenous infusions of methylprednisolone over one hour each day for 3 consecutive days. The dose was usually 1 gram/day for adults or 10 mg/kg/day for children.

The disease manifestations, full blood counts, serum creatinines, serum electrolytes, total complement levels, double stranded DNA levels were recorded prior to and in the first, second, fourth and twenty-fourth weeks following the pulse. Reversal or control of the disease manifestation/s after pulse therapy was considered successful therapy. Where pulse therapy was given for control of renal disease, reversal of deterioration in renal function or stabilisation of renal function (defined as 20% or less deterioration in serum creatinine levels) or the remission of proteinuria were taken as successful outcome. In non-renal disease improvement in symptoms or reversal of the disease manifestation was regarded as a successful outcome.

Complications during the first two weeks (early) and thereafter were documented.

Early (within the first month) and late mortality were also recorded.

PATIENTS

39 patients who fulfilled four or more of the 1982 ARA criteria for SLE were studied. Their ages ranged from 10 to 46 years, with a mean of 27.7 years.

There were thirty-eight females and one male.

Prior to pulse therapy the prednisolone doses ranged from nil to 1 mg/kg/day.

RESULTS

27 patients had renal indications for pulse therapy, 12 non-renal.

Out of the 27 patients with renal indications, 17 improved. 8 had improvement in renal function and

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proteinuria and 9 had reduction in proteinuria and oedema.

10 patients who improved had concomitant treatment with cytotoxic agents (4 had azathioprine, 6 cyclophosphamide). In addition 2 had peritoneal dialysis.

14 patients had renal biopsies done within a year prior to or subsequent to the pulse. 7 patients had WHO Class IV nephritis, 4 Class V nephritis, 2 Class II nephritis and one sclerosed glomeruli. Of the 7 who had Class IV nephritis, 6 improved with pulse therapy, while 3 out of 4 patients with Class V nephritis improved. Both patients with Class II nephritis improved (Table I).

Table I
PROFILE OF PATIENTS GIVEN PULSE METHYLPREDNISOLONE FOR RENAL LUPUS

Patient	Age	Imm	Indication Creat	Post-Pulse Creat & WHO Class	Renal Biopsy	Response	Comments
1	31	Aza	↓ Function Creat 5.5	9.3	Nil	No	Acute PD
2	31	Nil	↓ Function	4.0	Nil	No	Acute PD Died D7
3	42	Nil	↓ Function Creat 4.3	—	Nil	No	Died same day
4	28	Nil	Proteinuria Creat 1.7	2.0 0.6*	V post	Yes	iv Cyclo PTB 8 weeks
5	46	Nil	Proteinuria		Nil	Yes	—
6	22	Nil	↓ Function Creat 3.7	2.6	VI post	Yes	Cyclo Died 10 months
7	42	End	Proteinuria		V Pre	Yes	Cyclo Pneumocystis pneumonia Died 12 weeks
8	33	Aza	↓ Function Creat 6.2	5.0 6.2*	IV post	No	Aza, Cyclo Acute PD Died 8 weeks
9	10	Aza	↓ Function Creat 2.4	2.4	Nil	No	Died
10	33	Nil	Proteinuria		Nil	Yes	Died 7 weeks
11	17	Aza	↓ Function Creat 2.9	7.0	Nil	No	Septicaemia 8 weeks
12	10	Nil	Proteinuria	—	V pre	Yes	—
13	31	Cyclo	↓ Function Creat 4.1	3.4	Nil	No	Cyclo
14	18	Nil	Proteinuria		IV post	Yes	—
15	30	Nil	↓ Function Creat 6.2	1.1 1.2*	IV pre	Yes	Acute PD Aza
16	19	Nil	↓ Function Creat 5.0	6.4	Nil	No	Died D6
17	21	Aza	↓ Function Creat 1.7	3.6	Nil	No	Died D4
18	16	Nil	Proteinuria	—	IV post	Yes	—
19	18	Nil	↓ Function Creat 5.2	3.0 5.5*	IV pre	Yes	Cyclo Chronic PD
20	40	Nil	↓ Function Creat 4.8	1.4 6.8*	II	Yes	Aza Salmonella Gp B
21	18	Nil	↓ Function Creat 1.7	1.0	—	IV post	Yes
22	28	Nil	Proteinuria	—	Nil	Yes	Cyclo Aza Staph
23	22	Aza	↓ Function Creat 7.6	5.6 6.5*	Nil	No	iv cyclo
24	30	Nil	↓ Function Creat 3.8	5.8	Nil	No	Sepsis Died D12
25	27	Nil	↓ Function Creat 6.5	7.2	V pre	No	PD
26	31	Nil	↓ Function Creat 7.2	1.6	II pre	Yes	Acute PD Aza

Aza = azathioprine
Cyclo = cyclophosphamide
PD = peritoneal dialysis
* = creatinine results 4 weeks after pulse
Imm = immunosuppressive therapy
Function = deterioration in renal function
pre & post = pre and post methylprednisolone
Staph = staph aureus
D = day

All patients were female except for patient 12

Table II
PATIENTS GIVEN PULSE METHYLPREDNISOLONE FOR NONRENAL LUPUS

Name	Age	Imm	Indication	Response	Comments
1	28	Aza	Interstitial Lung Disease	No	Died same day
2	23	Nil	Pulmonary haemorrhage	Transient	Died D12
3	30	Nil	Interstitial Lung Disease	No	Died D15 Candida infection
4	30	Nil	Lupus gut	Yes	—
5	24	Nil	Disease Activity	No	Died D3 Gram negative sepsis
6	36	Cyclo	Choreoatrhetosis, Chorioretinitis	Yes	—
7	32	Cyclo	AIHA*	Yes	iv pulse cyclo
8	35	Nil	Disease Activity	Yes	Salmonella Gp C
9	35	Nil	CNS lupus	No	—
10	20	Nil	Pits	No	Died same day
11	13	Nil	Pulmonary Haemorrhage	Yes	Staph arthritis 16 weeks
12	26	Nil	CNS lupus	Yes	—

All patients were females

Imm = immunosuppressives
cyclo = cyclophosphamide
Aza = azathioprine
*AIHa = Auto-immune haemolytic anaemia
D = Day

12 patients received pulse methylprednisolone for non-renal lupus (Table II). 7 patients showed clinical response. The 5 patients who did not respond had interstitial lung disease, active disease and CNS lupus. One of the CNS lupus patients had fits followed by coma from which she succumbed. The other had cerebral infarction which rendered her bedridden.

No acute complications of pulse therapy were encountered. 11 patients had infections. 6 patients had infections occurring within the first month of pulse therapy. 4 of the 6 had bacterial infections and 2, fungal infection. Of the 4 who had bacterial infection, 1 had unspecified septicaemia, one gram negative septicaemia and 2 had Salmonella infection (one Group B and another Group C). Infections occurring after the first month of methylprednisolone therapy occurred in 5 patients due to pyogenic bacteria (2 patients), tuberculosis (1 patient), fungal (1 patient) and pneumocystis carinii (1 patient). 7 out of 11 patients (63.6%) with infection died. Of these 4 were from bacterial infection, 2 from fungal infection and one from pneumocystis carinii (Table III).

15 patients died. 8 deaths occurred within the first week of pulse therapy, 3 within the second week. The remaining 4 deaths occurred 4 weeks or more following the pulse. The causes of death could be classified as due to infection or disease. 7 of the early deaths resulted from disease, while 4 were due to infection. 3 of the late deaths were due to infection while only 1 was due to active disease (Table IV).

Table III
INFECTION AND CAUSATIVE ORGANISMS

Organism	No. of patients (%)
Pyogenic bacteria	7 (63.6)
Tuberculosis	1 (9.1)
Fungal	2 (18.2)
Pneumocystis	1 (9.1)

Table IV
TIMING OF DEATH IN RELATION TO METHYLPREDNISOLONE THERAPY

Time of death (week of pulse)	Cause of death: Disease (No of patients)	Cause of death: Infection (No of patients)
Day of pulse	4	0
1*	2	2
2	1	2
8	1	2
12	0	1

*Within 1 week but not on same day of pulse

DISCUSSION

Pulse doses of methylprednisolone have been administered to SLE patients when conventional therapies have failed or in situations when rapid administration of potent high dose steroids are required to control life threatening disease complications.

Difficulty in assessing the response to pulse methylprednisolone has been due to the dearth of controlled studies. Recently, Edwards (4) did a double blind controlled trial on 21 patients with renal and non-renal lupus and found no significant difference between the pulse and non-pulse groups.

Previous uncontrolled studies on pulse methylprednisolone focussed initially on its use for lupus nephritis. Kimberly (5) reported on 34 patients with lupus nephritis treatment with pulse methylprednisolone and found that 12 (35.3%) had a favourable response, which he defined as a 20 per cent or greater decline in serum creatinine, as compared with pre-treatment level. 9 of these 12 patients responded within 4 weeks of pulse therapy and all had responded within 2 months of the pulse. He found that those who responded favourably had recent deterioration in renal function but neither the degree of proteinuria nor content of the urinary sediment had any correlation with response to therapy. Patients responding to pulse therapy were more likely to have diffuse proliferative nephritis. In retrospective studies by Ponticelli (6) 27 patients with biopsy proven diffuse lupus nephritis were reviewed. 3 of the 4 patients with glomerular sclerosis progressed to renal failure and the fourth remained azotemic. Alkylating agents were also used in a number of the patients studied.

These observations seem to be borne out in our study of lupus nephritis patients who were pulsed. 15 (62.96%) out of 27 of our renal lupus patients improved with pulse therapy. The one patient whose renal biopsy showed sclerosis demonstrated transient improvement in renal function. Both patients with diffuse mesangioproliferative lupus nephritis improved. Unfortunately, data with respect to the rapidity of decline in renal function in the patients with class IV nephritis was not available, but 6 out of 7 of these patients improved. 10 patients showed improvement in renal function within the first week of pulse therapy but by the second week, one patient had further deterioration in renal function. By the fourth week, 8 patients had sustained improvement or stabilisation of their renal function which persisted till the twenty-fourth week.

The group of patients given pulse therapy for non-renal lupus in our study was small and diverse. 7 out of 12 (58.3%) responded. 2 patients who died on the same day of pulse therapy were admitted in a very ill state. Previous studies on the utility of pulse methylprednisolone in non-renal SLE have reported variable results (7-9). Occasionally, patients admitted in a very ill state with life threatening disease have responded dramatically to pulse methylprednisolone.

Acute complications of pulse methylprednisolone such as anaphylaxis, seizures, cardiac arrhythmias and sudden death were not encountered in our series of patients (10).

The complications encountered in our study were chiefly due to infection. In the majority of cases infection proved to be fatal. Late infections were probably related to the use of long term high dose steroids rather than pulse methylprednisolone. It is noteworthy that Salmonella septicaemia occurred in 2 of the 4 patients who had infection in the first month of pulse therapy. This organism has been reported to cause septicaemia more frequently in SLE patients (11).

It would appear that pulse methylprednisolone is useful in treating patients with acute deterioration of renal function and in non-renal lupus. The main reason advocated for its use is the rapid provision of high dose steroids while limiting their deleterious side effects. However the difficulties inherent in assessing its efficacy are due to its use in combination with other agents such as cytotoxic as well as oral high dose steroids and the paucity of matched controlled trials. Its usage must therefore be limited to patients whose disease manifestations are potentially reversible. However, the possibility of severe and even fatal infections must be borne in mind. The physician must be alert in detecting and aggressively treating these complications.

In conclusion, our study shows that pulse methylprednisolone is a useful adjunct in the therapy of lupus nephritis and in severe and life-threatening manifestations of non-renal lupus where conventional high dose oral corticosteroid may prove less effective.

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