Cyclophosphamide in systemic lupus erythematosus

T. HADIDI

From the Rheumatology Department, Maadi Hospital, Cairo, U.A.R.

Cyclophosphamide has been used in systemic lupus erythematosus (SLE) (Seah, Wong, Chew, and Jayaratnam, 1966) and beneficial results have been claimed. In experimental studies, cyclophosphamide prevents the occurrence of autoimmune disease in NZB mice which are unique in that they uniformly have a form of glomerulonephritis resembling human lupus nephritis (Schwartz, 1969). The drug is known to affect both lymphocytic and plasmocytic cell lines in their pathological forms and it also prevents the proliferation of immunoblasts (Turk, 1967). It consistently appears to depress the white blood count before any damage occurs to platelets or red blood cells. It can be administered orally since its absorption is very predictable (Dubois, 1966).

The controlled trial of a drug in a chronic but sometimes lethal disease such as SLE presents obvious difficulties and no such trial has ever been attempted. The author has nevertheless acquired considerable experience in the use of this drug during the past 5 years and a description of this experience is now presented.

Selection of patients

During the past 5 years 35 patients suffering from SLE have been admitted to hospital for assessment and treatment of their disease. All fulfilled the criteria for the diagnosis of SLE of Dubois (1966) and also the criteria proposed by Winslow, Ploss, and Loitman (1958) and modified by Willkens, Decker, and Wilske (1968).

All 35 patients were treated initially with prednisolone 40-60 mg. daily (Pollak, Pirani, and Kark, 1961) with subsequent reduction in dosage as indicated by their clinical condition.

Eight patients failed to respond to treatment, and in another four patients steroid administration was complicated by the development of posterior subcapsular cataract, duodenal ulcer, diabetes mellitus, and aseptic necrosis of the femoral heads. These twelve patients had a severe, active, and continuing form of the disease and are referred to as 'Group A'. There were eleven females

and one male and their ages at onset ranged from 16 to 38 years. They initially had very high erythrocyte sedimentation rates (over 90 mm./hr Westergren). The duration of illness on admission ranged from 1 to 9 years and all had renal involvement (proteinuria greater than 100 mg./litre of urine and granular casts).

The treatment of the remaining 23 patients was easier to manage and they thus constituted a more benign group. For purposes of comparison, twelve patients with renal involvement were selected from these 23 patients to form 'Group B'. These twelve patients were roughly comparable to those in Group A in terms of age, disease duration, and the presence of renal involvement, but their symptoms had been readily controlled with prednisolone and there were no complications of treatment.

Method

All the patients were assessed clinically on admission and at weekly intervals during their hospital stay.

The following investigations were carried out routinely: chest radiograph, blood count, blood urea, creatinine clearance, erythrocyte sedimentation rate (Westergren method), LE-cell tests, urine microscopy and quantitative estimation of albuminuria, serum protein electrophoresis, serological tests for syphilis, Waaler-Rose test, and electrocardiographs.

On discharge our patients were followed up for 2 years at 4-weekly intervals. They were advised to avoid pregnancy, an intrauterine device being recommended in preference to the oral contraceptive pill.

Use of cyclophosphamide

Cyclophosphamide was added to prednisolone for the patients in Group A, while the patients of Group B continued to take the steroid alone. Long-term therapy with relatively small doses was preferred to short intensive courses because such a plan is probably safer, produces fewer side-effects, and may be expected to produce more favourable clinical results (Fosdick, 1968). Cyclophosphamide was given in 50 mg. tablets at an initial loading dose of 2.5 mg./kg. body weight/day. A single daily increment of 50 mg. was added not less than 8 weeks after starting treatment. Clinical and laboratory evaluations were carried out weekly. If the white blood count fell below 2000/cu.mm., the drug was discontinued

for 2 or 3 days; this was usually sufficient for the count to rise again, when therapy would be re-instituted at a lower dosage.

Results

In those patients who appeared to respond to cyclophosphamide the time taken for improvement to occur varied from about 4 to 12 weeks. Improvement did not take place after this time even with prolonged administration.

GROUP A

At the end of twelve weeks there was evidence of improvement in nine of the twelve patients, with reduction of fever and tachycardia, and improvement in systemic signs of disease, such as skin rash, alopecia, arthralgia, and signs of cardiac, pulmonary, and neurological involvement. In these nine patients there was overall improvement in renal function and a quantitative decrease in proteinuria. In three patients it was possible to withdraw prednisolone, the other six being maintained on a small dose averaging 4 mg. daily. No correlation was apparent between response to cyclophosphamide and disease severity or duration.

GROUP B

There was a comparable improvement, but these patients had to be maintained on higher doses of prednisolone, averaging 10 mg. daily.

The features of the two groups before and after 12 weeks are shown in Table I.

Follow-up

The patients were assessed at further 4-weekly intervals for an average of 2 years.

GROUP A

The nine patients who had improved on cyclophosphamide alone or combined with steroids suffered no subsequent relapses. The three patients who failed to respond to cyclophosphamide were tried on other immunosuppressant agents. One of them nevertheless had a severe relapse (fever, arthritis, vasculitis, and pleurisy) responding only to a very high dose of steroids which had to be given in spite of the presence of a posterior subcapsular cataract. The other two patients died in uraemia.

GROUP B

Six patients had no relapses during the 2 years' follow-up period. In the other six, the dose of prednisolone had to be repeatedly increased for a time in four patients to tide them over frequent relapses. One patient died in rapidly developing renal failure and another from a massive haematemesis complicating a steroid-induced duodenal ulcer.

A comparison of the two groups after 2 years is shown in Table II.

Side-effects

These were never severe enough to warrant cessation of the drug. Bone marrow aplasia did not occur.

Table I *Comparison of both groups before and after 12 weeks treatment*

Group	A		B	
	At onset of trial	12 weeks later	At onset of trial	12 weeks later
Mean blood urea (mg. per cent.)	50	24	40	30
Mean albumin/24 hrs (mg.)	1,060	320	950	230
Mean ESR (mm./hr)	119	21	89	28
Mean haematocrit (per cent.)	32	38	34	35
Mean daily prednisolone (mg.)	50	4	30	10
Mean daily cyclophosphamide (mg.)	150	150	—	—

Table II *Comparison of both groups after 2 years*

Group	A	B
Mean blood urea (mg. per cent.)	35	30
Mean albumin/24 hrs (mg.)	250	210
Mean ESR (mm./hr)	20	19
Mean haematocrit (per cent.)	37	35
Mean daily prednisolone (mg.)	3	11
Mean daily cyclophosphamide (mg.)	50	—
Number of patients in remission for 2 years	9	6
Number who died in renal failure	2	1
Number who died from other causes	0	1

Infections, particularly candidiasis of the mouth, occurred in four patients but were never serious. During infections, leucocytosis occurred in spite of continued administration of cyclophosphamide. Treatment was with appropriate antibiotics. Hair thinning was transient and complete alopecia was not encountered.

Illustrative case histories

CASE 1

A 19-year-old male student had symptoms of SLE for 1 year. He was admitted to hospital in March, 1968, in a relapse, with fever, polyarthralgia, nephrotic syndrome, peripheral vasculitis, raised ESR (142 mm./hr), blood urea 80 mg. per cent., and albuminuria 4 g./litre. He had been receiving 60 mg. prednisolone daily for 2 months when 150 mg. cyclophosphamide was added to his daily treatment.

A remission took place in 6 weeks. He became well symptomatically, the ESR fell to 20 mm./hr, the blood urea to 30 mg. per cent., and the albuminuria to 1 g./litre, and the hypoalbuminaemia was corrected. On discharge he was taking 10 mg. prednisolone and 50 mg. cyclophosphamide daily. Contact with this patient was lost for a time but he was re-admitted 4 months later in another relapse. He stated that during this period he had discontinued treatment altogether.

It was now decided to try cyclophosphamide alone at a dose of 150 mg. daily and he made a remarkable improvement in 4 weeks. On discharge he was asymptomatic on 50 mg. cyclophosphamide daily and diuretics. His ESR was 22 mm./hr, blood urea 25 mg. per cent., and he was passing 1.5 g. albumin/litre of urine.

CASE 2

A 23-year-old female secretary had features of SLE with renal involvement for 4 years. She was admitted to hospital in December, 1966, in relapse, with fever, florid 'butterfly rash', cutaneous vasculitis, left basal pleurisy, arthritis with effusion in the knees, ESR 130 mm./hr, blood urea 40 mg. per cent., albuminuria 400 mg./litre, granular casts and strongly positive LE-cell test, packed cell volume 30 per cent.

She had been receiving 40 mg. prednisolone daily for 2 months when 150 mg. daily of cyclophosphamide was added. She went into a remission in 4 weeks and it was later possible to withdraw the prednisolone, continuing a maintenance dose of 50 mg. cyclophosphamide daily; 2 years later she was feeling well and cyclophosphamide was discontinued in 1968.

One year later she is still doing well, the latest ESR being 12 mm./hr, blood urea 20 mg. per cent., packed cell volume 38 per cent., albuminuria 300 mg./litre.

There were no side-effects due to cyclophosphamide in either case.

Discussion

There is a high incidence of spontaneous remission in cases of SLE (Dubois 1966), and it is emphasized that the experience presented in this report does not

form a controlled clinical trial; the patients in the two treatment groups were selected by their differing response to treatment with prednisolone, and there was no question of random allocation to cyclophosphamide therapy. It has, however, been shown that the patients treated with cyclophosphamide tended to improve and that the dose of prednisolone could be lowered to a greater extent than in those not receiving cyclophosphamide. This is all the more striking in view of the fact that patients in the cyclophosphamide-treated group were those who had failed to respond satisfactorily to prednisolone, or who had developed complications of treatment, and who therefore presented a more difficult problem in management.

Contrary to the experience of others (Fosdick, 1968), it was not necessary to induce leucopenia with cyclophosphamide before observing a clinical remission, and it may be that any beneficial effect of the drug is related to prolonged use rather than to a high dose.

Definite confirmation of the therapeutic efficiency of cyclophosphamide in SLE is still lacking, and we have as yet no clear idea of its mode of action in this disease. The present study nevertheless clearly demonstrates that it can be used safely and successfully over prolonged periods, and that it is therefore indicated, in the dosage schedule outlined, in patients with active SLE, particularly those in whom treatment with corticosteroids alone is unsatisfactory because of lack of response or the development of steroid side-effects.

A point of further interest is the relatively benign course followed by most patients in both treatment groups, particularly with regard to renal disease. All 24 patients studied had signs of renal involvement, but only three died in renal failure during a 2-year period of follow-up. The others have done well, the mean blood urea in both treatment groups falling during the first 12 weeks of treatment and remaining lowered thereafter. Proteinuria diminished correspondingly. Renal impairment, though an important cause of mortality in SLE (Larson, 1961; Dubois, 1966), is not therefore necessarily a cause for immediate concern.

Summary

Of 35 patients with systemic lupus erythematosus, eight failed to respond to prednisolone and four had complications of steroid treatment. These twelve patients were treated with prolonged cyclophosphamide in an initial dose of 2.5 mg./kg. body weight. Progress in these patients was compared with that of twelve others of comparable disease state, who were treated with prednisolone only, the mean length of follow-up being 2 years.

Improvement took place in most patients in both

treatment groups, but tended to be greater in those treated with cyclophosphamide, in whom a reduction of prednisolone dosage was also accomplished more satisfactorily. In the dosage schedule used, no serious toxic effects of cyclophosphamide were encountered.

All 24 patients had evidence of renal involvement but, although three died of renal involvement during the 2-year period, 21 did well, the mean blood urea and urinary protein falling in both treatment groups.

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