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Intensive immunosuppression versus prednisolone in the treatment of connective tissue diseases

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SUMMARY Intensive immunosuppression (IIS) was compared with prednisolone alone over a 2-year period in the treatment of severe connective tissue diseases. IIS consisted of 15 daily infusions of 750 mg antilymphocyte globulin (ALG), azathioprine 2·5 mg/kg/day, and prednisolone reducing from 150 mg, followed by maintenance azathioprine and prednisolone. The initial dose for prednisolone by itself was 60 mg and patients not responding to this regimen over a minimum of one month were then given IIS. Forty-one patients with life-threatening or severely disabling polyarteritis nodosa (PAN), dermatomyositis/polymyositis (DM), or systemic lupus erythematosus received one or other treatment. All 11 patients who received IIS for PAN remitted. Ten of these had renal impairment which was reversed or halted with IIS, and in 6 of these renal function had been deteriorating with prednisolone alone. One patient died of pneumonia in renal failure 9 months later but with PAN in remission. Two further patients, neither having renal involvement, achieved remission with prednisolone alone. Early cytotoxic treatment would seem to be indicated in PAN when there is renal involvement. Two patients with DM entered remission on prednisolone alone. The remaining 12, of whom 5 had failed steroid therapy, received IIS. Improvement or halting of deterioration was achieved in all 12 with best results in those without marked muscle wasting consequent to disease of long duration. The results suggest that IIS may be a useful adjunct in those patients failing to respond to prednisolone. IIS seemed no more effective than prednisolone alone in the treatment of the 14 patients with SLE and in particular lupus nephritis. Flares in disease activity were common in both groups and appeared to be related to prednisolone dosage. IIS was generally well tolerated, though infection occurred in 2 patients. Vertebral collapse or osteonecrosis of the femoral head occurred in 3 patients following IIS, all of whom had been previously receiving prednisolone for long periods.

Introduction

Cytotoxic drugs, usually given singly, are used in the treatment of connective tissue diseases with the aim of suppressing the abnormal immune mechanisms which appear to be significant in the pathogenesis of these diseases. Combinations of cytotoxic drugs are established as effective in the treatment of lymphoproliferative malignancies,[1 2] and such regimens may similarly benefit patients with connective tissue diseases. Moreover, the combination regimen of intensive immunosuppression (IIS) described below is demonstrably immunosuppressive in that it suppresses rejection of renal transplants.[3]

Selected patients with polyarteritis nodosa (PAN), dermatomyositis/polymyositis (DM), and systemic lupus erythematosus (SLE) treated in a pilot study with IIS appeared to improve and suffered no serious side effects. Accordingly further patients with these disorders were admitted to a second study, now in progress for 4 years, to compare the efficacy of IIS with prednisolone alone.

In this paper the response over the first 2-year period of patients receiving IIS in both studies is compared with that of patients receiving prednisolone by itself.

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Patients and methods

Patient selection. All patients were suffering from severely disabling or life threatening disease. Patients with DM and SLE fulfilled generally accepted diagnostic criteria.[4 5] Those with PAN had involvement of 2 or more organs, plus biopsy confirmation in half, all but one of the remainder having mononeuritis multiplex.[6] Patients in the comparative study were randomly allocated to either regimen, but those not responding to prednisolone after a minimum of one month were then given IIS.

Patient groups. The results are presented of both studies taken together and the patients are divided into 3 treatment groups: (1) patients receiving prednisolone alone; (2) patients receiving IIS having previously received no prednisolone or less than 60 mg/day for less than one month; (3) patients receiving IIS having failed to respond to prednisolone greater than 60 mg/day for more than one month.

It will be seen that those patients failing to respond to prednisolone are included in both first and third groups. The two groups receiving IIS are considered separately, as many patients had fulminant disease and previous prednisolone in high doses may have altered the response to IIS. Some patients included in the third group have received prednisolone outside the study and the data for this period are not given.

Treatment regimens are given in Table 1. Approval for the study was given by the Ethical Committee of Northwick Park Hospital. Patients gave informed consent before entering the study.

During the intensive phase of immunosuppression patients were isolated but not barrier nursed, and a trained nurse was in continuous attendance. The patients were carefully monitored for evidence of infection or reaction to therapy.

Patient assessment and presentation of data. Patients were assessed at 3-monthly intervals for 24 months. At each assessment clinical and laboratory parameters of disease were recorded on a score

Table 1 *Treatment regimens*

1. *Intensive immunosuppression*:	
Initial phase:	ALG—15 daily infusions of 750 mg in 500 ml saline over 5 hours
	Azathioprine—2·5 mg/kg/day to a maximum of 150 mg/day
	Prednisolone—150 mg/day orally reducing to 20 mg over 10 days
Maintenance phase:	Azathioprine and prednisolone in doses adjusted to disease activity
2. *Prednisolone alone*:	Prednisolone 60 mg/day taken as a single morning dose and adjusted according to disease activity

Table 2 *Scoring of clinical and laboratory parameters of disease activity*

(A) Polyarteritis nodosa		
Renal	2	Abnormal urinary sediment or 24 hour urinary protein 0·5–3 g (GFR normal)
	4	24 hour urinary protein >3 g or GFR >50%< normal.
	6	GFR <50%>25% of normal
	8	GFR <25% of normal
Muscle	1	Myalgia
	2	Myositis by biopsy or raised CPK or muscle swelling
Systemic	1	Unwell, at work
	2	Unwell, unable to work
	3	Fever or weight loss
Joints	1	Arthralgia
	2	Arthritis
Skin	1	Livido reticularis Purpura Urticaria Erythema nodosum
	2	Nail fold infarcts or biopsy-proved leucocytoclastic angitis or capillitis
	4	Vasculitic ulcers
Vasular insufficiency of digit or limb	1	Cyanosis, pallor, cold, rest pain, anaesthesia
	2	Threatened gangrene
	3	Gangrene
Respiratory	1	Asthma or impaired but improving vital capacity or gas transfer
	2	Pleuritic chest pain or pleural rub
	3	Fleeting radiological opacity
	4	Falling gas transfer or vasculitis on lung biopsy
Gut	1	Mild abdominal pain
	2	Severe abdominal pain
	3	Infarcted bowel
Hb	1	9–12 g/l
	2	<9 g/l
ESR	1	20–50 mm/h
	2	>50 mm/h
(B) Dermatomyositis		
*Weakness	1	Mild proximal
	2	Moderate proximal
	3	Severe proximal
	4	Bulbar, neck or respiratory weakness
Muscle biopsy	1	Fibrosis, atrophy
	2	Moderately severe changes without necrosis
	3	Severe changes with necrosis but without inflammatory infiltrate
	4	As for 3 with inflammatory infiltrate
EMG	1	Minimal change
	2	Definite myopathic changes
CPK		(Normal–10 U/l)
	1	80– 200 U/l
	2	200– 500 U/l
	3	500–1000 U/l
	4	>1000 U/l
(C) Systemic lupus erythematosus		
Renal Muscle Systemic Joints		As for PAN
Skin	1	Butterfly rash without follicular plugging or photosensitivity or urticaria
	2	Rash with follicular plugging

(*Table 2 contd.*)

CNS	2	Affective disorder
	4	Epileptiform seizures
	6	Persistent neurological signs
	8	Altered consciousness
Vasculitis	1	Purpura
	2	Vasculitic ulceration
Respiratory	1	Abnormal but improving vital capacity or gas exchange
	2	Fleeting radiological opacity (not infectious)
	4	Falling vital capacity or gas exchange
Hb	1	9–12 g/l
	2	<9 g/l
ESR	1	20–50 mm/h
	2	>50 mm/h
DNA binding	1	30–60% (normal <30%)
	2	>60%

*Compiled from modified MRC muscle charts.

devised to quantitate disease activity, vital organ involvement being given double loading (Table 2). The results for the three treatment groups are shown separately. The composite scores of disease activity for each patient are represented graphically, as are the drug treatments.

Results

Details of the patient groups are shown in Table 3.

POLYARTERITIS NODOSA (Fig. 1)
Eight patients received prednisolone alone, and in 6 of these there was progressive deterioration in renal function over weeks or months (mean 6·5 months). Following IIS renal function improved steadily in 5 and deterioration was halted in the sixth. The cumulative score was falling in one patient at the time of withdrawal, and this was accounted for by improvement in nonrenal parameters (myositis, arthritis, and cutaneous vasculitis), while serious renal impairment remained unchanged at grade 8. Of the 5 patients receiving IIS de novo 4 had renal involvement, which improved in 3 after treatment. It remained static in the fourth, who needed chronic haemodialysis and died of bacterial pneumonia 9 months later. At the time of death, and in the months prior to it, there was no evidence clinically of active PAN, and he was taking prednisolone 10 mg daily. At post-mortem there was no evidence of active vasculitis. One patient has residual mild hypertension.

Advancing digital gangrene was arrested following IIS in all 3 patients with this feature, one having failed to respond to prednisolone. In those given prednisolone alone the dosage of 50 mg at 3 months was double that of those given IIS.

DERMATOMYOSITIS/POLYMYOSITIS (Fig. 1)
Nine of 12 patients improved substantially following IIS, whereas 5 of these had failed to respond to 60 mg prednisolone alone given for between 2 and 12 months. The rate of improvement was most rapid in those not previously receiving prednisolone. Three other patients had long-standing disease with severe muscle weakness and wasting, with fibrosis on biopsy, progressing despite low-dose prednisolone. Deterioration was halted and creatine phosphokinase (CPK) fell following IIS, but there was little increase in muscle power. All patients having IIS were receiving less than 12 mg prednisolone by 2 years, but cytotoxic drugs were withdrawn in only 2 patients.

In 2 of the patients given prednisolone alone dis-

Table 3 *Details of patients studied*

Diagnosis		*PAN*			*DM*			*SLE*	
*Treatment groups**		*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*
Numbers	Male	7	4 (1)	5	2 (1)	3 (1)	2	1	2
	Female	1	1	1	2	4 (1)	3 (1)	4	7
Age	Mean	45	45	50	50	55	42	46	36
	Range	17–68	18–64	17–68	30–64	29–70	32–62	35–64	18–64
Mean duration of disease before entering study (months)		4	6	8	11	14	40	30	53
Prednisolone before entering study	Number	0	1	6	2	2	5	1	4
	Mean Dosage (mg)	0	30	37	12	12	50	10	6
	Mean duration (months)	0	2	9	5	15	33	6	21

Numbers in brackets indicate associated malignancy.
*A = Prednisolone alone. B = IIS, previous prednisolone <60 mg over < one month. C = IIS having failed prednisolone >60 mg over > one month.

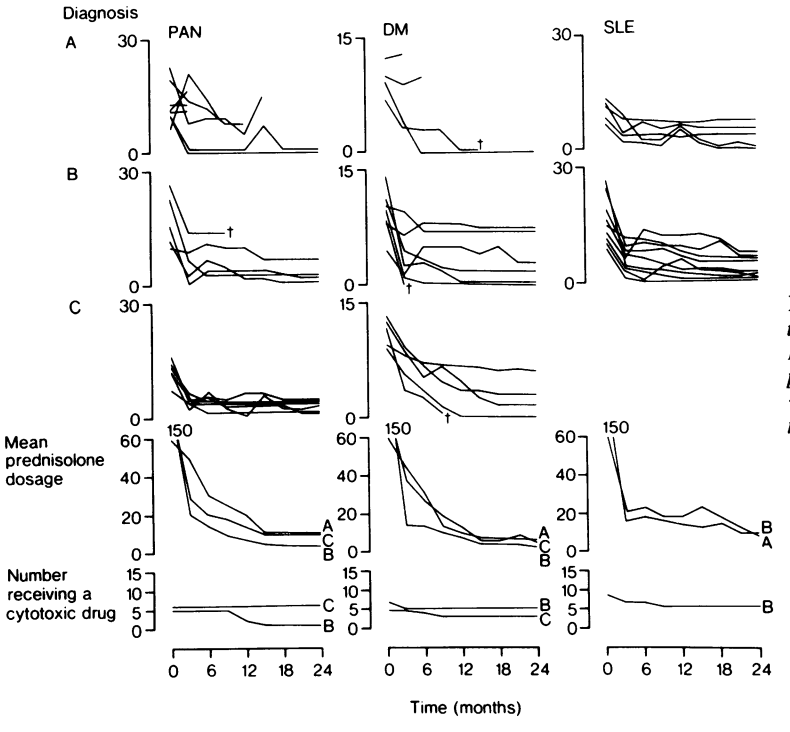

Fig. 1 *Cumulative score and drug therapy plotted against time. A: Prednisolone alone. B: IIS, previous prednisolone <60 mg <one month. C: IIS, previous prednisolone >60 mg >one month.*

ease remitted completely within one year. However, 2 others failed to respond despite 3 or more months of 60 mg prednisolone but improved markedly following IIS.

One patient in each group died of malignancy. Carcinoma of the pancreas became manifest after starting prednisolone in one, and the other 2 carcinomas of the breast and bladder respectively were known to be disseminated at the time of starting IIS. In all 3 patients myositis was in remission at time of death. A fourth patient remains well 6 years after resection of carcinoma of the breast.

SYSTEMIC LUPUS ERYTHEMATOSUS (Fig. 1)

On entering the study the patients receiving IIS all had a higher composite score than those receiving prednisolone. No patient failed to respond to prednisolone, and after 2 years there was no difference between the score in the 2 groups. Prednisolone dosage was the same, though 6 of the 9 given IIS were continuing with cytotoxic drugs.

Moderate renal involvement (score greater than 4) was seen in half of both groups and remained unaltered by therapy. Haemolytic anaemia and joint, muscle, and lung involvement improved promptly and substantially on starting either treatment; systemic features, rashes, and vasculitis tended to flare on reduction of prednisolone in both groups.

SIDE EFFECTS (Table 4)

Two patients with SLE were given IIS while being treated for pre-existing septicaemia, and one of these developed meningitis from the same organism after completing a 2-week course of antibiotics. In one other patient infected gangrene caused septicaemia during the intensive phase of immunosuppression. All infections responded to intensive antibiotic therapy. Persistent fevers were common and treated presumptively as infection.

Table 4 *Side effects*

ALG (32 patients, 5 withdrawals)		
	Recurrent fevers/rigors	6
	Urticaria, rashes	6
	Serum sickness	2
	Septicaemia	2
	Acute hypotension	1
Azathioprine (32 patients, 14 withdrawals)		
	Dyspepsia	4
	Hepatitis	2
	Marrow suppression	2
	Hypogammaglobulinaemia	2
	Recurrent infections	2
	Drug fever	2
Cyclophosphamide (10 patients, none withdrawn)		
Prednisolone	Osteonecrosis of hip	1
	Vertebral collapse	2
	Steroid myopathy	1
	Insulin dependent diabetes	1

The course of ALG was completed in over three-quarters of the patients, the remainder receiving at least 5 infusions. No patient showed hypersensitivity to horse serum on skin testing prior to the course of antilymphocyte globulin (ALG), and acute hypotension, which may have been anaphylactic, occurred in only one patient.

Transient high fevers and rashes responded to antihistamine and/or hydrocortisone intravenously.

Azathioprine was withdrawn in one-third of patients owing to side effects, which were reversible, and the substituted cyclophosphamide was well tolerated. Serious side effects of prednisolone were seen only in patients given IIS, though the majority had received steroid therapy for long periods before entering the study.

Discussion

In the past high-dose corticosteroid alone has been recommended as intitial treatment of PAN, improving the 5-year survival from 13% to 43%.[7] More recently cyclophosphamide was shown to result in dramatic improvement in 16 patients with PAN.[8] Azathioprine has also been used with varying success,[6 9] though the dose may be critical.

Our results suggest that IIS is more effective than prednisolone alone in the treatment of PAN, particularly if there is renal involvement. Furthermore, as all 10 patients receiving this treatment remained in remission for 2 years with no major relapses, it would appear that azathioprine at 2·5 mg/kg/day is an effective cytotoxic drug in such circumstances. However, all but 3 patients were receiving a cytotoxic drug at the end of 2 years, and the correct duration of maintenance therapy remains to be established.

There are few adequately controlled, prospective studies on the use of corticosteroids or cytotoxic agents in the treatment of DM. An extensive retrospective analysis[10] indicates that corticosteroids significantly improve power and lower serum CPK, though the authors stress that the natural history of untreated disease is not known. More recently in a prospective study azathioprine at 2 mg/kg/day in combination with prednisolone did significantly improve function after 3 years.[11] Cyclophosphamide and chlorambucil may be useful adjuncts,[10 12] and, although beneficial, methotrexate was found by one group to cause serious side effects.[13]

There are too few patients receiving prednisolone alone in this study to comment on its role in the initial treatment of DM. However, an additional benefit of cytotoxic therapy may be inferred from the improvement following IIS in those deteriorating while on prednisolone. Remission was nevertheless seen with prednisolone alone: this response appears to be associated with the absence of central migration of nuclei on initial muscle biopsy.[14]

Muscle power did not increase in those patients with marked muscle wasting after long-standing disease. However, deterioration halted after IIS, and had this been given earlier greater improvement might have been expected.

The many published reports do not agree on the efficacy of individual cytotoxic drugs in SLE. Azathioprine at 2·5 mg/kg/day appeared to be beneficial in 16 of 35 patients,[15] but this could not be confirmed in 2 further studies with higher[16] and lower[17] doses. Despite the initially encouraging results of the NIH 10-week study of cyclophosphamide in the treatment of lupus nephritis,[18] at longer follow-up the differences between the groups was minimal. A further randomised, prospective study of 39 patients with lupus nephritis over 6 months with cyclophosphamide showed no significant difference in renal parameters.[19] Furthermore, combinations of low-dose azathioprine and cyclophosphamide offered no additional benefit in terms of efficacy than 'full-dose' (2·5 mg/kg/day) azathioprine, and side effects of cyclophosphamide were not avoided.[20] Most controlled studies of cytotoxic agents in SLE include prednisolone in both the placebo and cytotoxic groups. In this study IIS appears no more effective than prednisolone alone in the treatment of SLE and particularly lupus nephritis.

The intensive phase of immunosuppression was generally well tolerated and caused no untreatable side effects. The recrudescence of infection in one patient suggests that all but trivial infections should be treated long term. Anaphylaxis to ALG was rare and immune nephritis not seen.

Prednisolone caused the only serious irreversible long-term side effects. In each case it was given as part of IIS but following long-term steroid therapy, which might have been reduced had IIS been given earlier.

Although side effects to azathioprine were frequent they were reversible, and the substituted cyclophosphamide was well tolerated. It is impossible to say whether any of the cytotoxic drugs enhanced or induced neoplasia in those patients with malignancy or whether it has serious long-term complications.

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