PAPERS AND ORIGINALS

Controlled Trial of Azathioprine and Prednisone in Chronic Renal Disease

REPORT BY MEDICAL RESEARCH COUNCIL WORKING PARTY

British Medical Journal, 1971, 2, 239-241

Summary

Patients with various forms of glomerulonephritis, but excluding those with minimal glomerular changes, were admitted to a controlled trial of a regimen which combined azathioprine in a dosage of 2.5 mg/kg/day with prednisone in a dosage of 20 mg/day (adults) or 0.5 mg/kg/day (children). Of 149 patients included, 32 of them under the age of 15, 72 were randomly allocated to the "treatment" group and 77 to the "control" group. There was no evidence of benefit from the treatment group as a whole; and the mortality was in fact higher in the treated group.

Introduction

There is evidence from several sources—on animal experiments, the deposition of immune globulin in glomeruli in various types of glomerulonephritis in man, and the formation of soluble complexes and complement consumption—that abnormal immunological responses may be involved in various forms of chronic renal disease, including some which manifest themselves as the nephrotic syndrome. As the limitations of steroid therapy have become more widely appreciated interest has grown in other immunosuppressive agents, including cytotoxic drugs (*British Medical Journal*, 1970).

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The report was prepared by Professor G. A. Rose and Professor D. A. K. Black.

The trial now reported was set up by a Medical Research Council Working Party; it was designed as a pilot study, in which a comparison was to be made between patients treated with a combination of azathioprine and prednisone, and patients not so treated; patients likely to respond to prednisone alone—that is, those with minimal glomerular changes—were not included in the trial. As indicated in the methods section, patients suffering from a wide range of renal disorders were included, in the hope of identifying a group of patients responding to this combined treatment, which might then be investigated in a larger trial. In the event, no such group was identified; this essentially negative result on a substantial number of patients has already been mentioned (Rose, 1970) as a correction to an unduly optimistic comment on the outcome of the trial made before the actual results were known (*British Medical Journal*, 1970).

Methods

Patients of any age were considered clinically acceptable for the trial if they had persistent proteinuria of 1 g or more per 24 hours, provided that renal failure was not severe—that is, creatinine clearance rate not less than 20 ml/min—and that none of the following conditions was present: (1) certain specified diseases (diabetic nephropathy, polyarteritis nodosa, systemic lupus erythematosus, pyelonephritis); and (2) previous treatment with immunosuppressive drugs, other than corticosteroids.

Patients not so excluded underwent a four-week period of preliminary observation, during which a renal biopsy was performed. Sections from all patients in the trial were sent to Professor D. B. Brewer, who classified them into four groups: (1) Membranous changes only; (2) proliferative changes, with or without capillary wall thickening; (3) minimal or no changes; and (4) other changes. This classification followed the same principles as in the previous trial of steroids in the nephrotic syndrome (Black *et al.*, 1970). Patients were accepted for the present trial only if they fell into one of the first two pathological groups listed above.

Patients and their Management

From October 1967 to October 1969 149 patients were accepted for the trial (32 children under the age of 15 and 117 adults of average age 34.2 years). These were allocated randomly to treatment and control groups. The numbers in the various groups, classified according to the renal biopsy appearances and the clinical syndrome with which they presented, are given in Tables I and II.

TABLE I—Numbers of Patients Entering the Trial, Classified by Age and Pathological Group

Age Group	Renal Biopsy Classification	No. of Patients	
		Treatment	Control
Children	Membranous	0	1
	Proliferative	16	15
Adults	Membranous	5	9
	Proliferative	51	52
Total		72	77

TABLE II—Classification of Patients by the Clinical Syndrome with which they Presented

Clinical Syndrome	No. of Patients	
	Treatment	Control
Symptomless proteinuria	19	17
Nephrotic syndrome	29	35
Proteinuria with some renal failure	12	10
Rapidly progressive nephritis	12	15
(including Henoch-Schönlein syndrome)	(5)	(7)

Patients allocated to the treatment group received azathioprine in a dosage of 2.5 mg/kg/day, together with prednisone 20 mg/day for adults or 0.5 mg/kg/day for children. This treatment was continued for a minimum of eight weeks. Continuation thereafter was at the discretion of the physician, and its duration was variable. In 50 patients (10 children and 40 adults) it was continued for a total period of six months. No

bone marrow depression or serious infective complications were recorded.

Immunosuppressive drugs (steroid or other) were not given to patients in the control group. In other respects there were no restrictions on treatments in either group, though efforts were made to avoid systematic differences in management.

Results

Follow-up ceased in June 1970. At this time all patients had been followed for at least six months after entering the trial. Some results are also given for the second six months, though the follow-up period specified in the protocol was for six months only. Since there was only one child with "membranous" changes this case has been excluded from the analysis.

The initial status and progress of the 31 children with "proliferative" changes are summarized in Table III. There is a tendency to higher leucocyte counts in the treatment group, probably attributed to prednisone. There is no evidence of diminution in proteinuria or improvement in renal function during the first six months. During the second six months an apparent benefit in creatinine clearance rates is just significant at the 5% level.

Results for the 14 adults with membranous glomerulonephritis are summarized in Table IV. There are no noteworthy differences between the two groups at any stage. Beyond six months the numbers were too small for analysis.

Results for the 103 adults with proliferative glomerulonephritis are given in Table V. IgG levels tend to be lower, and white blood counts are significantly higher, in the treatment group. In other respects the groups behave very similarly.

The numbers of deaths and transfers to long-term haemodialysis are given in Table VI. For purpose of analysis these have been added together, as in the previous trial (Black *et al.*, 1970). The treatment group has fared worse, notably from renal failure. The excess mortality is unlikely to have been due to chance: for the six-month point adopted in the trial design, $P < 0.01$ by the Wilcoxon two-sample test, beyond six months the incomplete follow-up and small numbers precluded worthwhile testing of significance.

TABLE III—Initial Status and Progress of Children in the "Proliferative" Group: Mean Values (and Standard Errors) of Various Characteristics

	Preallocation		0-2 Months		2-6 Months		6-12 Months	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
No. alive and examined in period	16	15	16	15	16	14	9	8
Systolic B.P.	112.2 (+3.1)	115.3 (+4.7)	118.1 (+4.9)	113.0 (+4.4)	120.7 (+4.6)	113.6 (+5.0)	113.3 (+5.3)	117.9 (+3.4)
Creatinine clearance (ml/min)	74.3 (+8.3)	60.6 (+7.4)	75.1 (+12.1)	54.8 (+6.8)	80.6 (+14.6)	66.8 (+9.0)	92.1* (+10.4)	62.5* (+10.2)
Proteinuria (g/24 hr)	3.2 (+0.7)	2.1 (+0.5)	2.2 (+0.7)	2.7 (+0.9)	1.7 (+0.4)	1.5 (+0.7)	1.3 (+0.6)	2.2 (+1.5)
Plasma albumin (g/100 ml)	3.0 (+0.3)	3.1 (+0.3)	3.6 (+0.3)	3.1 (+0.3)	4.3 (+0.4)	3.6 (+0.3)	3.8 (+0.6)	3.5 (+0.4)
Plasma urea (mg/100 ml)	31.1 (+3.7)	34.1 (+3.8)	45.3 (+12.4)	35.3 (+6.2)	65.5 (+24.5)	36.6 (+5.8)	25.0 (+1.8)	34.3 (+5.8)
Haemoglobin (g/100 ml)	11.8 (+0.4)	11.4 (+0.5)	12.3 (+0.6)	11.5 (+0.5)	12.1 (+0.8)	12.2 (+0.6)	12.6 (+0.8)	12.9 (+0.5)
W.B.C./mm ³	7,900 (+500)	7,500 (+500)	10,900* (+1,600)	7,100* (+600)	8,100 (+700)	7,300 (+800)	5,100 (+400)	7,100 (+700)
IgG (mg/100 ml)	729 (+165)	1,080 (+622)	613 (+126)	1,047 (+212)	798 (+213)	Small Nos.†	572 (+114)	Small Nos.†

* $0.05 > P > 0.01$.

† IgG results were not available on all patients. The smaller number of patients at 6-12 months is due partly to loss from death or transfer and partly to difficulty in follow-up.

TABLE IV—Initial Status and Progress of Adults in the "Membranous" Group: Mean Values (and Standard Errors) of Various Characteristics. (Numbers beyond 6 Months too Small for Analysis)

	Preallocation		0-2 Months		2-6 Months	
	Treatment	Control	Treatment	Control	Treatment	Control
No. alive and examined in period	5	9	5	9	5	8
Systolic B.P.	146.0 (+9.3)	133.3 (+3.5)	140.0 (+11.0)	129.4 (+5.6)	146.0 (+10.4)	133.6 (+8.2)
Creatinine clearance (ml/min)	65.8 (+20.5)	105.3 (+6.3)	77.0 (+25.4)	94.2 (+6.7)	86.0 (+23.7)	76.5 (+6.7)
Proteinuria (g/24 hr)	6.4 (+1.6)	9.8 (+1.6)	6.2 (+2.4)	8.9 (+1.1)	5.2 (+1.7)	9.9 (+2.6)
Plasma albumin (g/100 ml)	2.3 (+0.2)	2.4 (+0.2)	2.9 (+0.4)	2.4 (+0.2)	3.2 (+0.3)	2.6 (+0.2)
Plasma urea (mg/100 ml)	52.0 (+10.8)	31.3 (+2.0)	58.0 (+11.7)	38.2 (+1.8)	55.2 (+13.8)	40.8 (+4.0)
Haemoglobin (g/100 ml)	13.2 (+1.0)	14.7 (+0.3)	10.8 (+1.3)	14.3 (+0.5)	12.4 (+0.9)	13.9 (+0.4)
W.B.C./mm ³	9,200 (+500)	8,700 (+800)	7,800 (+800)	8,100 (+800)	10,400 (+1,400)	8,500 (+700)
IgG (mg/100 ml)	991 (+470)	408 (+40)	557 (+280)	567 (+100)	585 (+140)	640 (+70)

(No significant differences)

TABLE V—Initial Status and Progress of Adults in the "Proliferative" Group: Mean Values (and Standard Errors) of Various Characteristics

	Preallocation		0-2 Months		2-6 Months		6-12 Months	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
No. alive and examined in period	51	52	50	52	45	52	23	34
Systolic B.P.	142.5 (+2.7)	145.7 (+3.1)	144.5 (+3.0)	143.8 (+3.1)	146.2 (+4.0)	139.3 (+3.0)	133.8 (+4.8)	144.2 (+3.9)
Creatinine clearance (ml/min)	79.7 (+5.6)	70.7 (+4.2)	80.4 (+5.8)	75.0 (+5.8)	81.3 (+5.9)	70.2 (+5.9)	76.2 (+7.8)	78.8 (+6.7)
Proteinuria (g/24 hr)	6.0 (+0.7)	6.0 (+0.6)	5.9 (+0.7)	5.9 (+0.8)	5.0 (+0.7)	5.8 (+0.8)	4.0 (+0.7)	4.1 (+0.8)
Plasma albumin (g/100 ml)	3.1 (+0.2)	3.1 (+0.1)	3.4 (+0.2)	3.3 (+0.1)	3.3 (+0.1)	3.2 (+0.1)	3.4 (+0.2)	3.4 (+0.2)
Plasma urea (mg/100 ml)	53.1 (+5.3)	53.7 (+3.7)	71.9 (+11.7)	55.8 (+4.2)	61.2 (+8.5)	64.3 (+6.8)	57.4 (+8.2)	62.2 (+9.0)
Haemoglobin (g/100 ml)	12.3 (+0.3)	12.7 (+0.3)	12.2 (+0.3)	12.3 (+0.3)	12.9 (+0.3)	12.5 (+0.3)	13.4 (+0.6)	12.9 (+0.4)
W.B.C./mm ³	7,700 (+300)	7,700 (+300)	8,800* (+400)	7,300* (+300)	8,700 (+400)	7,800 (+300)	6,900 (+500)	7,400 (+400)
IgG (mg/100 ml)	725 (+70)	951 (+100)	688 (+70)	928 (+110)	680 (+80)	898 (+80)	700 (+90)	885 (+100)

* P < 0.01.

TABLE VI—Numbers of Deaths and Transfers to Dialysis

Cause of Death/Dialysis	0-6 Months		>6 Months		Total	
	Treatment	Control	Treatment	Control	Treatment	Control
Renal failure	7	1	0	3	7	4
Other	2	0	2	0	4	0
Total	9*	1*	2	3	11	4

* P < 0.01 (Wilcoxon 2-sample test).

Some details of individual patients who died or were transferred to dialysis are given in Table VII. Necropsy was performed in four of the fatal cases. These results underline the apparently high risk to patients in the treatment group during the early months of the trial, when all of them were receiving azathioprine and prednisone. All deaths and transfers to dialysis occurred in patients with proliferative glomerulonephritis. They were patients with initially poor renal function (who were by chance rather more numerous in the treatment group).

TABLE VII—Some Details of Deaths and of Transfers to Dialysis

	Months in Trial	Age	Sex	Cause of Death
Treatment group	<1	30	M.	Myocardial infarction
	1	16	M.	Renal failure
	2	43	F.	Acute pancreatitis
	2	21	F.	(Dialysis)
	3	23	M.	(Dialysis)
	4	7	M.	Renal failure
	4	13	M.	Renal failure
	5	50	M.	Renal failure
	6	32	M.	(Dialysis)
Control group	9	55	M.	? Hypertension
	17	62	M.	Myocardial infarction
	3	13	F.	(Dialysis)
	7	43	F.	(Dialysis)
	10	61	M.	Renal failure

Discussion

The results suggest that the combination of azathioprine and prednisone is not likely to be effective in any large number of patients with chronic renal disease, and that the combination

is not without a risk of harmful effects. In another controlled trial of a similar combination of drugs in the treatment of children with the nephrotic syndrome (Abramowicz *et al.*, 1970), no significant benefit was obtained, when compared with prednisone alone, either in patients who were steroid-resistant or in those who responded to prednisone but relapsed frequently. This negative finding has, of course, no bearing on the effectiveness of a similar regimen in the quite different situation of cell-mediated transplant rejection, nor does it preclude the possibility of benefit in individual patients with one or other form of renal disease. Moreover, the apparent failure of one particular combination of agents has no real significance as evidence against an immunological hypothesis for the aetiology of renal disease; neither, of course, does it give any support.

Cyclophosphamide has been found much more effective for relapsing steroid sensitive patients, who mostly show minimal changes on renal biopsy (Moncrieff *et al.*, 1969; Barratt and Soothill, 1970), but not, apparently, for patients who have structural glomerular lesions which are steroid-resistant (White *et al.*, 1970). A further trial incorporating this agent, by itself and also in combination with heparin, in patients with rapidly progressive nephritis is currently in progress.

The Medical Research Council wishes to thank the following, who very kindly assisted by submitting cases for inclusion in the trial or by attending meetings of the Working Party: Dr. I. M. Anderson, Dr. T. M. Chalmers, Professor J. O. Forfar, Professor R. S. Illingworth, Dr. J. H. Jones, Dr. J. G. G. Ledingham, Dr. Mary McGeown, Professor W. F. O'Dwyer, Dr. P. Sharpstone.

The Council also thanks Professor I. Doniach and Dr. Mary MacDonald, who reviewed all the pathological material with Professor Brewer; and Mrs. C. Rose for help in the administration and analysis of the trial.

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