

AGGRESSIVE TREATMENT WITH PULSE METHYLPREDNISOLONE OR PLASMA EXCHANGE IS JUSTIFIED IN RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

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Summary

Rapidly progressive crescentic glomerulonephritis (RPGN) carries a poor prognosis, but early immunosuppression may reverse renal impairment. We have given intensive therapy to 27 patients with biopsy proven RPGN from 1977–1981. Fourteen patients received pulse methylprednisolone (PMP) and 13 patients plasma exchange (Px). These patients fared significantly better than 17 patients seen from 1972–1979 who had neither PMP nor Px. Both groups received oral prednisolone and other immunosuppressive agents. PMP and Px were equally effective in prolonging survival without dialysis and had no serious side effects; prognostic factors affecting the outcome of treatment were identified. Early aggressive immunosuppressive therapy is indicated in RPGN.

Introduction

Several recent studies have reported the successful treatment of rapidly progressive glomerulonephritis (RPGN) using pulse methylprednisolone (PMP) and/or plasma exchange (Px), with a better outcome following early intervention [1–5].

Forty-four patients with biopsy-proven RPGN were seen in Liverpool between 1972 and 1981. The effects of PMP and Px were assessed in 27 matched patients seen from 1977–1981, and their outcome compared with that of 17 patients receiving oral immunosuppression alone, seen from 1972–1979.

Patients and methods

RPGN was defined as follows:

- a) Rapidly progressive renal failure with doubling of plasma creatinine concentrations (pCr) over 12 weeks;
- b) Normal sized kidneys on IVP;

TABLE 1. Clinical details of 44 patients with rapidly progressive crescentic glomerulonephritis. Patients' age, length of history, blood pressure and plasma creatinine concentration at presentation expressed as mean \pm standard deviation, with the range indicated in parentheses

	Sex M F	Age (years)	Length of history (weeks)	Associated disease	Blood pressure (mmHg)	Urine volume 0–500mls >500mls	Plasma creatinine concentration (μ mol/L)
Group A (17)	11 6	37.1 \pm 17 (13–66)	8.2 \pm 5 (4–24)	7	167/97 \pm 25/17 (130/70–210/130)	10 7	1097 \pm 513 (234–2000)
Group B (27)	23 4	53.5 \pm 15* (18–72)	9.2 \pm 7.5 (1–24)	14	158/90 \pm 17/10 (130/70–190/105)	15 12	835 \pm 397 (199–1756)
B1 methylprednisolone (14)	12 2	59.2 \pm 14 (20–72)	10.6 \pm 7.8 (1–24)	5	170/90 \pm 13/11	7 7	748 \pm 345 (256–1438)
B2 plasma exchange (13)	11 2	47.5 \pm 13.5 (18–61)	7.8 \pm 7.3 (1–24)	9	150/90 \pm 11/9	8 5	914 \pm 437 (199–1756)
TOTAL = 44	34 10	47.2 \pm 18 (13–72)	8.7 \pm 6.7 (1–24)	21	160/93 \pm 13/3	25 19	936 \pm 459 (199–2000)

* Difference between Group B and Group A significant (Students t = 3.260, p < 0.01)

- c) Proliferative glomerulonephritis with > 50 per cent glomeruli showing epithelial crescents and sclerosis.

Proven cases of systemic lupus erythematosus, post streptococcal glomerulonephritis and malignant hypertension were excluded, but 21 patients with polyarteritis nodosa (12), Wegeners granulomatosis (5), Goodpastures disease (3) and Henoch-Schönlein purpura (1) were included.

Two groups were studied:

- A) 17 patients given neither PMP nor Px;
B) 27 patients treated initially with either:
a) *methylprednisolone* (14 patients) 1g in 250ml five per cent dextrose i.v. over 30 minutes once on each of four consecutive days; or
b) *plasma exchange* (13 patients) 4–10 daily exchanges of 2–3L of plasma, replaced by PPF, over 7–14 days.

All patients in Group B, and 12 of 17 in Group A, received oral immunosuppression: prednisolone 30–60mg daily with azathioprine and/or cyclophosphamide (1–2mg/kg/day).

The groups are comparable in terms of sex, length of history, blood pressure, presence of extra-renal manifestations, and oligo-anuria (Table I). Patients in Group A were younger than in Group B and had a slightly higher plasma creatinine, possibly reflecting changes in referral and dialysis criteria over the ten years.

In Group B the 14 patients given PMP were in every respect comparable to the 13 given Px.

Sixteen patients in Group A and 16 in Group B had > 70 per cent crescents. The other 11 patients in Group B, and one in Group A had a milder lesion histologically with 50–70 per cent crescents, notwithstanding their rapidly progressive clinical course.

Results

No serious side effects of treatment with PMP or Px were seen.

Figure 1 shows that 18 patients in Group B had recovered after one month, whereas in Group A nine still needed dialysis. After one year only one patient in Group A did not need dialysis by comparison with 17 in Group B. Two patients in Group B were oliguric at presentation and required haemodialysis for six weeks and three months, before making a good recovery. Both were alive and well off dialysis three and four years after treatment with PMP.

The benefit from treatment with PMP or Px is still apparent when patients in Group B with histologically milder disease are excluded. Of 16 patients in Group B with > 70 per cent crescents, nine were off dialysis after one month by comparison with only six in Group A. After one year, only one of 16 patients in Group A with severe glomerulonephritis was off dialysis, by comparison with seven such patients in Group B ($\chi^2 = 6.0$, $p < 0.02$).

In Group B, patients given PMP did as well as patients given Px in terms of survival and recovery of renal function (Figure 2).

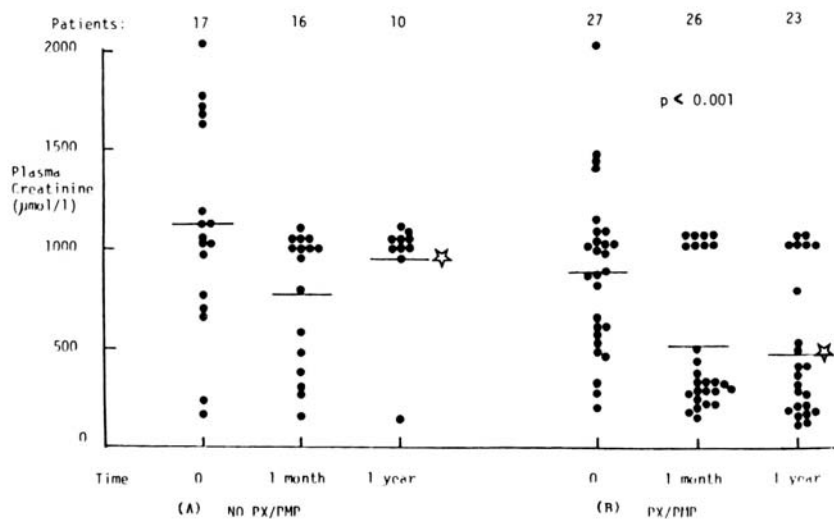


Figure 1

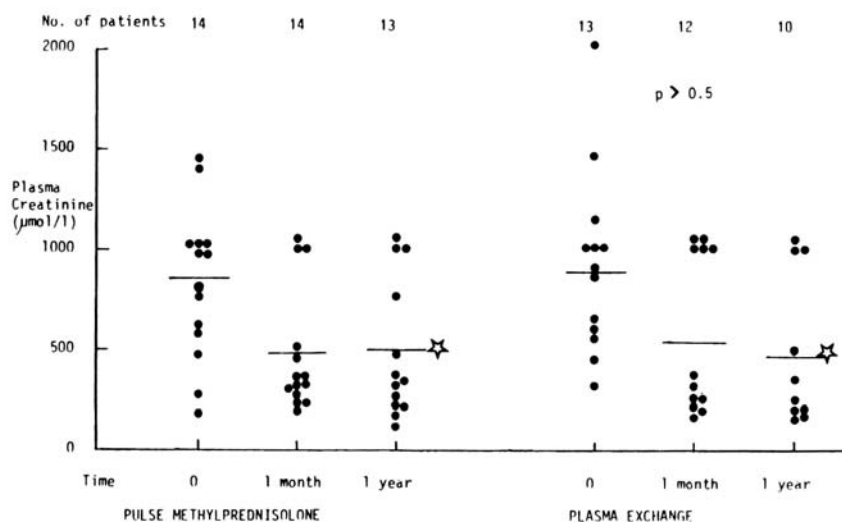


Figure 2

Factors at presentation associated with a favourable response three months after either form of therapy in Group B are shown in Table II. Patients who responded were older, and had a longer history, with more associated disease. A

TABLE II. Clinical details of Group B patients, comparing those who recovered renal function (19) and those who did not recover renal function (8). Patients' age, length of history, blood pressure and plasma creatinine concentration expressed as mean \pm standard deviation, with the range indicated in parentheses

Group B	Sex		Age (range)	Length of history (weeks)	Associated disease	Blood pressure	Urine volume		Plasma creatinine concentration μ mol/L	Percentage crescents			Immunofluorescence Ig/C Nil	
	M	F					0-500 mls	>500 mls		50-69	70-89	90-100		
Recovery renal function (19)	17	2	56 \pm 13.6 (18-72)	11 \pm 7.5 (2-24)	13	158/90 \pm 17/11	8	11	849 \pm 401 (278-1756)	10	6	3	6	6
No recovery renal function (8)	6	2	48 \pm 17 (20-61)	5.3 \pm 6.1* (1-20)	** 1	163/92 \pm 18/7	7	*** 1	798 \pm 411 (199-1408)	1	2	*** 5	3	1
TOTAL (27)	23	4	53.5 \pm 15 (18-72)	9.2 \pm 7.5 (1-24)	14	158/90 \pm 17/10	15	12	834 \pm 397 (199-1756)	11	8	8	9	7

Significance of differences between the mean, or proportions, of those who recovered renal function and those who did not recover renal function:

* (Students t = 2.066, p < 0.05)

** (χ^2 = 7.052, p < 0.01)

*** (χ^2 = 7.667, p < 0.01)

**** (χ^2 = 4.698, p < 0.05) (> 90 vs < 90%)

favourable response occurred more frequently in patients with a greater urine volume, a lower plasma creatinine and a milder glomerular lesion. Of 11 patients who had < 70 per cent crescents, 10 recovered, by contrast with only three of eight patients with > 90 per cent crescents. The presence of immunoglobulin and complement in the glomeruli did not affect prognosis.

Discussion

Immunosuppressive therapy for RPGN has been used for some years [6]. Recent reports of early, intensive treatment with PMP and/or Px have not established which is more effective or whether they are better than early conventional oral immunosuppression [1–5]. The rarity of RPGN makes studies difficult; a randomised, prospective controlled trial would have to be conducted on a national or international scale, and because of the clear advantages in some patients it may be unethical to withhold therapy. For these reasons we have compared treated patients with a comparable group of historical controls.

In our series, patients with RPGN given either PMP or Px fared significantly better in terms of survival and the need for permanent dialysis than patients receiving oral therapy alone. The superiority of these treatments is still seen when only patients with > 70 per cent crescents are considered, a comparison which is necessary because more patients in Group B had milder disease histologically. Patients given PMP were well matched with patients given Px for age, length of history, associated disease, residual renal function and histological severity. Since Px was no better than PMP and is more expensive, labour intensive and invasive, we now use PMP as the treatment of choice.

Favourable prognostic factors determining response to PMP/Px were milder disease at presentation, longer history and presence of extra-renal manifestations, suggesting that these cases may belong to a separate group. Nevertheless some patients with aggressive disease, advanced renal failure and a fulminant course responded well, even though recovery was delayed for several weeks. In such cases it is vital that therapy is not withdrawn prematurely. The advantages of early diagnosis and prompt treatment in all patients with RPGN cannot be overstated.

Acknowledgments

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References

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Open Discussion

DAVISON (Chairman) Thank you very much Dr Stevens for that very interesting communication. I think you ought to be congratulated on so clearly defining the group that you are studying although it does still appear to be very heterogeneous and I wonder if, when you are including such people as those with polyarteritis, how you actually made that diagnosis?

STEVENS The diagnosis was made on clinical grounds and also, if we had a suspicion that polyarteritis nodosa was the diagnosis we went ahead and performed renal angiograms before doing the biopsy looking for microaneurysms, but of twelve cases who had polyarteritis, we only did angiograms in about seven or eight and only about half of those were positive.

DAVISON These were the nodosa form or the microscopic form?

STEVENS We thought that these were microscopic polyarteritis.

OHNA (Tokyo) You stressed the beneficial effect in cases which showed negative immunofluorescence in renal biopsy. How do you explain this point?

STEVENS We in fact re-analysed some of our data including a much more thorough histological examination and that included the immunofluorescence studies. It would appear on the analysis that in fact it did not make a difference to the prognosis which is contrary to much of the literature which has been recorded, where in many cases those who have responded well to treatment have often been those with negative immunofluorescence.

STRANDGAARD (Copenhagen) How did you decide when to use plasma exchange and when to give pulse doses of methylprednisolone?

STEVENS When we commenced this study of looking at aggressive treatment in 1977 we were intending to use a randomised study with pulse methylprednisolone and plasma exchange but unfortunately logistically it was not possible. There were fourteen patients given pulse methylprednisolone and thirteen given plasma exchange without any randomisation but when we looked at the groups they were entirely comparable retrospectively.

STRANDGAARD So there was no difference between the two groups.

STEVENS No there was not.

STRANDGAARD Are you surprised at this result, the identical result of the two kinds of treatment?

STEVENS Not particularly surprised but I am pleased that pulse methylprednisolone seems to be as effective as plasma exchange, because as far as patients and staff are concerned it is a lot less labour intensive, it is more pleasant for the patient and is much more easy to organise.

CASTRO (Munich) You are doing always infusion pyelogram before the treatment. How do you know that some patients do not have contrast nephropathy and that your therapy is having a beneficial effect on the contrast nephropathy?

STEVENS This is possible, but I cannot comment on this other than to say it is a possibility.