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Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies

CHARLES D. PUSEY, ANDREW J. REES, DAVID J. EVANS, D. KEITH PETERS, and C. MARTIN LOCKWOOD

Departments of Medicine and Histopathology, Royal Postgraduate Medical School, Hammersmith Hospital, London, England, United Kingdom

Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. To determine whether plasma exchange was of additional benefit in patients treated with oral immunosuppressive drugs for focal necrotizing glomerulonephritis (without anti-GBM antibodies), we performed a randomized controlled trial with stratification for renal function on entry. Forty-eight cases were analyzed, 25 in the treatment group (plasma exchange, prednisolone, cyclophosphamide and azathioprine) and 23 in the control group (drug therapy only). There was no difference in outcome in patients presenting with serum creatinine < 500 μmol/liter ($N = 17$), or > 500 μmol/liter but not on dialysis ($N = 12$), all but one of whom had improved by four weeks. However, patients who were initially dialysis-dependent ($N = 19$) were more likely to have recovered renal function ($P = 0.041$) if treated with plasma exchange as well as drugs (10 of 11) rather than with drugs alone (3 of 8). Long-term follow-up showed that improvement in renal function was generally maintained. The results of this trial confirm that focal necrotizing glomerulonephritis related to systemic vasculitis responds well to immunosuppressive drugs when treatment is started early, and suggest that plasma exchange is of additional benefit in dialysis-dependent cases.

Focal necrotizing glomerulonephritis (FNGN) is a severe form of glomerular inflammation which, if left untreated, usually progresses to end-stage renal failure in weeks or months—a syndrome known as rapidly progressive glomerulonephritis (RPGN) [1]. It is characterized pathologically by the presence of segmental proliferative and necrotizing lesions of glomerular capillaries associated, in most instances, with compression of the glomerular tuft by cellular "crescents" [2]. The processes leading to this pathological appearance are not fully understood, but may involve both humoral and cellular autoimmune mechanisms, and occur in a variety of clinical settings. The lack of understanding of underlying mechanisms has hampered the development of rational forms of treatment, which has generally depended on the use of cytotoxic drugs to control the abnormal immune response and corticosteroids to reduce inflammation.

The recognition that RPGN could be caused by autoantibodies to the glomerular basement membrane (anti-GBM disease or Goodpasture's syndrome) [3] led to the introduction of plasma exchange (PE) [4], which allowed rapid removal of circulating anti-GBM antibody before the effects of immunosuppressive drugs developed. Current results using this approach demonstrate greater improvement in renal function in Goodpasture's syndrome [5] than that reported in earlier series [3]. Because of the successful use of PE in anti-GBM disease, a similar therapeutic regimen was adopted in RPGN associated with other diseases, especially Wegener's granulomatosis (WG) and microscopic polyarteritis (MP) [6]. The demonstration in these patients of circulating autoantibodies to neutrophil cytoplasm (ANCA) [7, 8], and more recently to glomerular and other vascular endothelium [9–11], provides a further rationale for this approach. Uncontrolled results suggested a benefit from this form of treatment in systemic vasculitis [12], but as the use of cyclophosphamide and steroids without PE was also reported to be effective [13], a randomized controlled trial of the use of PE (in addition to immunosuppressive drugs) was established in 1978.

In this trial, we recruited patients with FNGN related to systemic vasculitis within the spectrum of "polyarteritis" [14], including those with idiopathic (I) RPGN [15, 16], but excluded cases with other defined immunopathology. Patients were stratified according to renal function at presentation, in order to allow separate analysis of the response in patients with varying severity of disease.

Methods

Patients

Patients with evidence of impaired renal function, renal biopsy showing FNGN with crescents, and a clinical diagnosis of WG, MP or IRPGN as previously described [15, 17, 18], were considered as candidates for the trial. Patients with anti-GBM disease and those with other defined causes of vasculitis (such as systemic lupus erythematosus, Henoch-Schönlein purpura) were excluded, as were cases with evidence of underlying chronic glomerulonephritis. Patients who had previously been treated with intravenous methylprednisolone, oral cyclophosphamide or PE were also excluded, although prior oral steroid therapy was permitted.

Fifty-two consecutive patients fulfilling the diagnostic criteria were stratified for severity into groups depending on renal

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function at the start of treatment. The most severe group was categorized as "dialysis-dependent" rather than oliguric, since this was a more practical approach. Criteria for starting dialysis were conventional for acute renal failure and included oligo-anuria, severe fluid overload or hyperkalemia, and serum creatinine approaching 1000 μmol/liter; these remained consistent throughout the trial. Patients were allocated to treatment (PE and drugs) or control (drugs alone) arms of the trial by random numbers. Treatment was started within 24 hours of clinical diagnosis. The randomization procedure ensured that patients in different arms of the trial were equally distributed throughout its course.

Investigations

All patients had initial standard hematological and biochemical profiles, including tests of renal and hepatic function. Creatinine clearance was estimated in cases not on dialysis. In addition, complement C3, C4 and CH50, and autoantibodies to GBM and dsDNA were measured, in order to exclude anti-GBM disease and systemic lupus erythematosus. Hepatitis B surface antigen was not detected in any case. Renal biopsies were processed for light and electron microscopy and direct immunofluorescence, and reported by a single observer (DJE) without knowledge of the clinical diagnosis or response to treatment. Subsequently, renal function was monitored by serum creatinine or creatinine clearance as clinically indicated, with assessment points at one, 2, 6 and 12 months and annually thereafter.

Treatment

It was not considered necessary to include a "sham" PE treatment protocol. Control patients received induction therapy to 8 weeks of: (1) prednisolone 60 mg daily, reducing by 15 mg at weekly intervals to 30 mg daily, then by 5 mg at weekly intervals to 20 mg daily, and subsequently more slowly as clinically indicated; (2) cyclophosphamide 3 mg/kg daily; (3) azathioprine 1 mg/kg daily. Patients over 55 years were given cyclophosphamide 2 mg/kg daily and no azathioprine, because of the increased risks of immunosuppression. Cytotoxic drugs were temporarily discontinued if leucopenia ($< 4 \times 10^9$/liter) occurred, or in the presence of severe intercurrent infection. After 8 weeks, cyclophosphamide was stopped in those patients in remission and azathioprine dosage increased to 2 to 3 mg/kg daily for maintenance therapy, together with tapering doses of prednisolone. Treatment was normally continued for at least one year, after which attempts were made to discontinue it.

The PE group received identical drug therapy, together with at least five, 4 liter exchanges for 5% albumin (plasma protein fraction, PPF) within the first week. Two units of fresh frozen plasma (FFP) were given at the end of the exchange to restore clotting factors only if there was overt haemorrhage, or within 48 hours of renal biopsy or surgery. Fresh plasma was used infrequently and in small volumes, so a separate analysis of its effect was not possible. The total number of exchanges was determined by the clinical response, and a mean of nine procedures was performed (range 5 to 25). Vascular access was achieved by cannulation of antecubital veins whenever possible; central venous cannulation was sometimes required and rarely arterio-venous shunts were used. All plasma exchanges were performed on a discontinuous-flow cell centrifuge (Hemonetics).

Table 1. Patients analyzed in the trial

	Treatment (25)	Control (23)
Age *years*	18–76 (52)	14–69 (51)
Sex (M:F)	16:9	14:9
Diagnosis (WG:MP:I)	10:11:4	13:9:1

Definition of improvement

This was defined as a fall in serum creatinine of > 25% (or a rise in creatinine clearance of > 25% in cases with initial serum creatinine <150 μmol/liter) for patients not on dialysis at presentation; and as recovery of renal function independent of dialysis in those patients already on dialysis. In non-dialysis-dependent patients, the change in serum creatinine was also compared in each arm of the trial. This assessment was made at one month from the start of treatment. Follow-up data were obtained at 2, 6 and 12 months and then annually.

Statistical analysis

The difference in outcome at one month between patients in each arm of the trial, in the three stratified groups, was determined by a two-tailed Fisher's exact test. Numbers in the trial, based on a preliminary analysis at five years [19], were designed to avoid overlooking a 60% difference in response between control and treated patients on dialysis, at a level of significance of 5% using a test with a power of 95%. The degree of improvement in renal function, in the groups not on dialysis, was compared by analysis of co-variance using serum creatinine at presentation and at one month. The percentage of crescents and of sclerosed glomeruli in the dialysis-dependent groups was compared by the Mann-Whitney U test.

Results

The details of the analyzed cases are shown in Tables 1 and 2. The effect of treatment on renal function could not be analyzed in four patients who died within two weeks. There were two early deaths in the treatment group (lung hemorrhage 1, septicemia 1) and two in the control group (lung hemorrhage 1, septicemia 1), all occurring in patients who were dialysis-dependent and gravely ill at presentation.

The outcome of the trial at one month is shown in Table 3. There was no significant difference in outcome between treatment and control arms for patients with initial creatinine <500 μmol/liter or >500 μmol/liter, but a greater number of dialysis-dependent cases treated with PE recovered renal function ($P = 0.041$, two-tailed Fisher's exact test). Analysis of co-variance revealed no significant difference in the degree of recovery of renal function at one month between treatment and control groups of non-dialysis patients (Figs. 1 and 2).

There was no apparent difference in distribution between treated and control patients with respect to age, sex or diagnosis, in any of the three strata of renal function. Renal biopsy results are summarized in Table 4, and show similar findings in treated and control patients at each level of renal function. There was wide individual variation in histology, but both groups contained comparable numbers of patients with the

Table 2. Long-term outcome of patients in the trial

Sex	Age at presentation	Diagnosis	Cr at pres/ days on dialysis	Cr at 1 year	Cr current or at death[a]	Time to ESRF *years*	Time of FU or to death[a] *years/months*	Comment
Treated patients								
Cr < 500								
M	55	MP	343	151	150[a]	—	7[a]	Myocardial infarct
M	71	WG	358	135	264[a]	—	7	I = P/A
F	18	MP	385	100	D	5	8	Dialysis
M	70	WG	363	174	167[a]	—	4[a]	Myocardial infarct
F	60	WG	130	122	409[a]	—	8[a]	Cardiac failure
M	36	MP	141	109	106	—	6	Independent
M	47	MP	336	198	133	—	4	I = P/C
M	69	MP	239	124	141[a]	—	2[a]	Pneumonia
M	46	I	310	150	119	—	8	Independent
Cr > 500								
F	30	WG	975	160	970[a]	1	1[a]	Renal failure
F	37	WG	581	208	T	9	11	Transplant
M	26	MP	572	242	T	3	10	Transplant
M	68	I	564	215	450[a]	1	5[a]	Pneumonia
M	62	MP	636	155	147	—	7	I = P/A
Dialysis dependent								
M	61	MP	1581(8)	445	811[a]	—	3[a]	Myocardial infarct
F	59	I	815(6)	124	N/A	—	3[a]	Pulmonary embolus
M	52	WG	1842(1)	129	194	—	8	I = P/A
F	68	MP	1138(1)	310	530	—	8	Independent
M	54	MP	1405(2)	187	238	—	6	I = A
F	66	WG	1250(1)	212	203	—	3	I = P/A
F	23	WG	1084(13)	D	D[a]	0	4[a]	Pneumonia
M	39	WG	1752(4)	N/A	N/A	—	3 (month)	I = lost to follow-up
M	39	WG	1310(1)	—	600[a]	—	2 (month)[a]	Lung hemorrhage
F	76	I	990(10)	—	471[a]	—	3 (month)[a]	Septicemia
M	73	MP	735(1)	—	376[a]	—	2 (month)[a]	Pneumonia
Control patients								
Cr < 500								
F	43	WG	384	81	97	—	9	I = P/A
M	63	WG	368	339	D	4	8	D = A
F	60	WG	447	220	T	4	10	Transplant
M	47	MP	488	274	672	—	7	Independent
F	48	WG	95	81	90	—	8	I = P/C
F	55	WG	321	80	107	—	4	I = P/C
M	48	WG	445	138	T	4	5	Transplant
M	37	MP	359	—	592[a]	—	4 (month)[a]	Subarachnoid
Cr > 500								
F	14	MP	562	87	71	—	10	Independent
M	45	WG	592	121	100	—	9	Independent
M	35	MP	632	154	T	4	10	Transplant
F	67	MP	600	195	201	—	4	Independent
M	16	MP	742	157	230	—	5	I = P/A
M	53	WG	620	150	150	—	4	I = P/C
M	65	WG	1100	—	619[a]	—	1 (month)[a]	Lung hemorrhage
Dialysis dependent								
F	58	WG	NA(4)[b]	248	450[a]	—	6[a]	Pneumonia
M	69	I	1629(1)	D	D[a]	0	1[a]	Renal failure
M	51	WG	600(1)	150	150	—	5	I = P/C
F	53	MP	803(0)	177	150	—	3	Independent
F	54	MP	946(5)	—	D[a]	0	3 (month)[a]	Pneumonia
M	60	WG	909(1)	—	D[a]	0	1 (month)[a]	Pneumonia
M	56	MP	931(1)	—	D[a]	0	1 (month)[a]	Myocardial infarct
M	66	WG	442(0)[c]	—	D[a]	0	1 (month)[a]	Lung hemorrhage

Abbreviations are: D, dialysis; T, transplant; I, independent renal function; P, prednisolone; A, azathioprine; C, cyclophosphamide.
[a] Renal function at death or time to death
[b] No creatinine available before dialysis, value on transfer after 4 days was 338 μmol/liter
[c] Dialysis started for oliguria and fluid overload

same degree of histological damage. The dialysis-dependent groups were examined closely for any differences in severity of disease (including glomerular pathology) or management, and none were detected (Tables 2, 4 and 5). In particular, there was no significant difference in the extent of crescent formation or glomerulosclerosis between treatment and control groups.

Table 3. Improvement in renal function at one month

	Treatment (25)	Control (23)
Creatinine <500 μmol/liter	9/9	7/8
Creatinine >500 μmol/liter	5/5	7/7
Dialysis-dependent[a]	10/11	3/8

[a] $P = 0.041$, Fisher's exact test

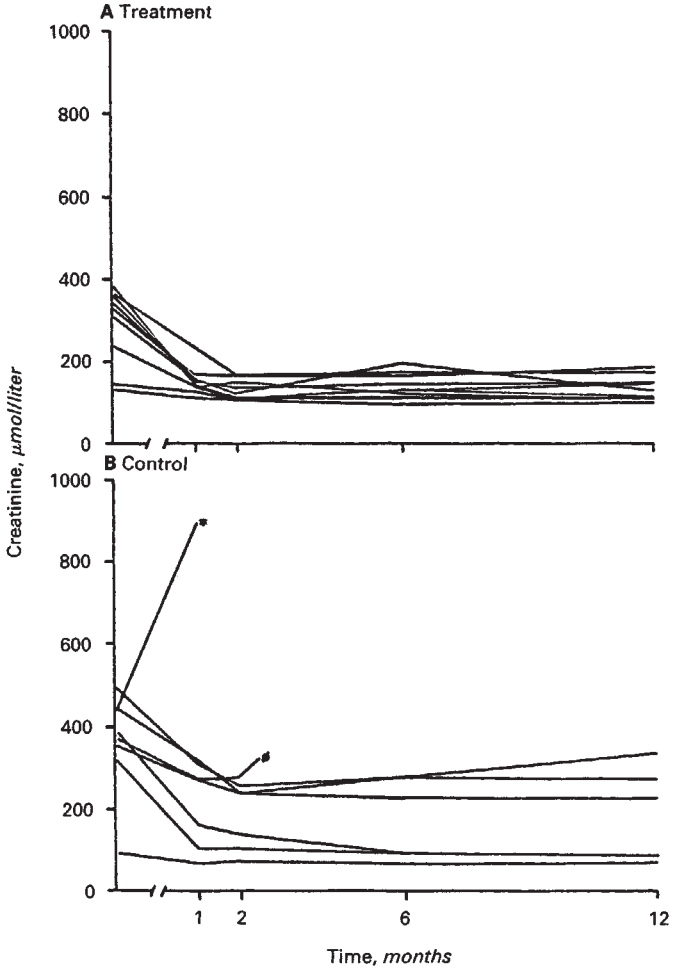

Fig. 1. *Serial serum creatinine levels in patients presenting with creatinine < 500 μmol/liter.* Symbols are: (ø) died; (*) withdrawn from trial and treated with PE.

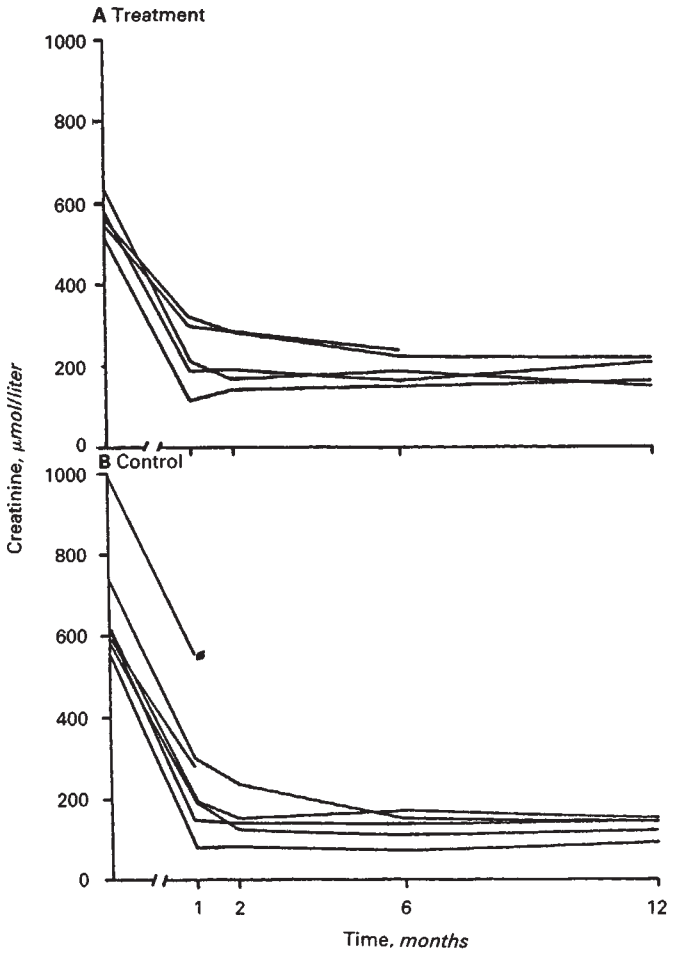

Fig. 2. *Serial serum creatinine levels in patients presenting with creatinine > 500 μmol/liter.* Symbol ø means the patient died.

Renal function was followed annually, and serial data to one year for individual patients are shown in Figure 1 (creatinine < 500 μmol/liter), Figure 2 (creatinine >500 μmol/liter) and Figure 3 (dialysis-dependent). The improvement in renal function achieved in both treatment and control patients was generally maintained. However, a further nine cases died between one month and one year, three treatment and six control. The principal causes of death in these patients with severe multisystem disease were: treatment group—lung hemorrhage 1, pneumonia 1, septicaemia 1; control group—lung hemorrhage 2, pneumonia 2, myocardial infarction 1, subarachnoid hemorrhage 1.

Long-term follow-up of surviving patients (from 3 to 11 years) confirmed that successfully treated patients generally maintained independent renal function unless the disease relapsed. Of patients followed for more than one year, eight developed end-stage renal failure (treatment 4, control 4), at 1, 3, 5 and 9 years in the PE group and during the fifth year in all cases in the control group. There were ten further deaths, unrelated to active vasculitis, which was not surprising considering the age of the patients. Details of the long-term outcome of individual patients are given in Table 2.

Discussion

This trial was started in 1978 in order to determine whether PE, a relatively new form of therapy at that time, would be of additional benefit in patients with FNGN without anti-GBM antibodies treated with cytotoxic drugs and steroids. The exclusion of patients with other immunopathologically defined forms of nephritis, such as systemic lupus erythematosus or Henoch-Schönlein purpura, was justified by their differing natural history and response to treatment. Unlike anti-GBM disease, in which the introduction of PE improved the outcome so considerably that we did not regard a controlled trial to be appropriate, RPGN associated with systemic vasculitis was reported to respond to drug therapy alone [13]. Since our early

Table 4. Summary of renal biopsy findings

	Treatment			Control		
Glomerular pathology %	< 500	> 500	RDT	< 500	> 500	RDT
Circumferential crescents	13	44	56	20	21	38
	(0–58)	(0–61)	(0–100)	(0–59)	(0–46)	(0–75)
Partial crescents	18	14	13	27	42	18
	(0–33)	(5–24)	(0–41)	(10–42)	(31–60)	(10–30)
Total sclerosis	8	17	15	11	7	20
	(0–23)	(0–59)	(0–67)	(0–63)	(0–15)	(0–50)
Partial sclerosis	24	2	6	15	5	12
	(0–83)	(0–5)	(0–67)	(0–38)	(0–20)	(0–27)
All of above	63	77	90	73	75	88

Note: For each feature the mean percentage and range is shown in the different groups.

Table 5. Details of dialysis-dependent patients

	Treatment (11)	Controls (8)
Age *years*	23–76 (55)	51–66 (58)
Sex (*M:F*)	6:5	5:3
Diagnosis (*WG:MP:I*)	5:4:2	4:3:1
Prior steroids (*cases*)	3	3
Dialysis before entry *days*	1–13 (4)	0–5 (2)
Dialysis after entry *days*[a]	1–31 (11)	7–14 (11)
Crescents plus sclerosis %	60–100 (90)	40–100 (88)

[a] In patients who recovered

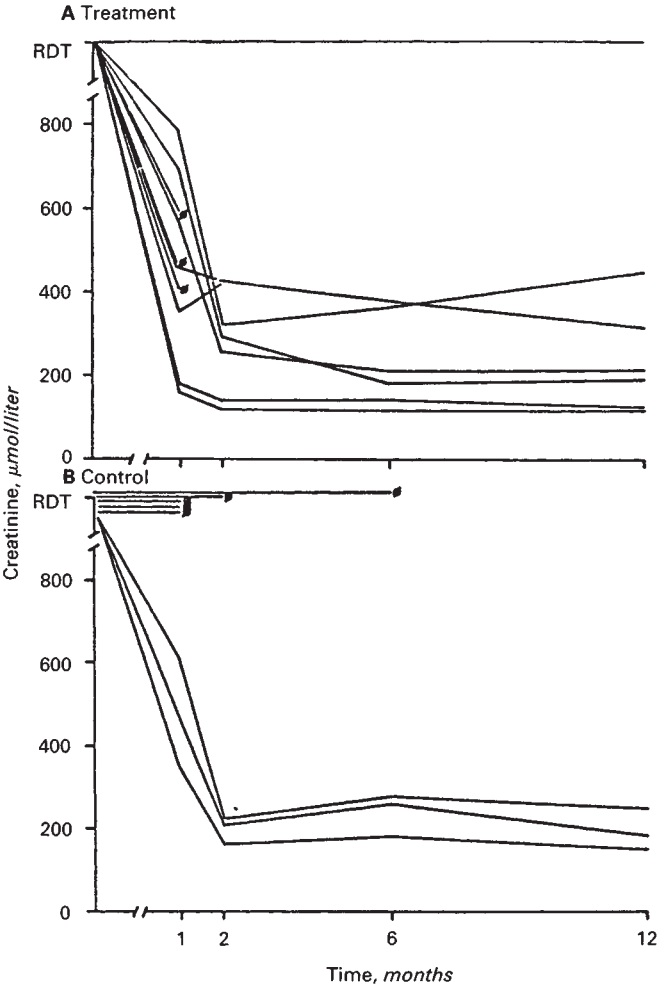

Fig. 3. *Serial serum creatinine in patients who were dialysis-dependent.* ø = died.

observations suggested a possible role for PE in such cases, especially in those with advanced disease [12], the trial was designed to compare outcomes in groups of patients with different degrees of renal impairment.

The decision to include patients with WG, MP and IRPGN was based on their histological and immunopathological similarities on renal biopsy, and on our experience of their response to treatment. The recent review of RPGN by Couser [1] supports this concept, and emphasises the close similarities between "renal vasculitis" [20] and "idiopathic RPGN" [21]. There is increasing evidence that patients with FNGN, with or without systemic vasculitis, show a similar response to immunotherapy when matched for renal function [22–25]. Although we were unaware of the relevance of ANCA at the start of the trial, it has now become clear that these autoantibodies are detectable in the different diagnostic groups included [7, 8, 15, 16], providing further support for their similarity.

Uncontrolled studies of such patients have generally reinforced our initial impression of the value of PE in advanced cases [26–28]. One recent controlled trial, however, failed to show a benefit of PE in RPGN [29]. In this study, the patient groups selected and treatment regimens were different to our own, and cases were not stratified for renal function. Other uncontrolled series have indicated that the use of high-dose intravenous methylprednisolone may also be more effective than conventional therapy in advanced disease [30–32]. Of note is the recent study by Bolton and Sturgill, who found that 16 of 23 patients became independent of dialysis following pulse methylprednisolone compared with 0 of 9 receiving various oral agents [32].

The trial has taken 10 years to complete, during which time there have been various improvements in management, including new antibiotics and more advanced renal and respiratory support techniques, though patients in both arms of the trial will have benefited similarly. An important factor, when compared with other trials [29], is that our study has been performed in a single center with the same group of physicians supervising treatment, thus ensuring similar management throughout, including criteria for dialysis. Side-effects of PE were few and generally minor, and technical difficulty never prevented treatment. The trial was not designed to examine the effect of PE on extra-renal manifestations of systemic vasculitis, because of

difficulties in assessment, but it was our impression that they improved more rapidly when PE was used. The relatively high overall mortality in the trial reflects the severity of disease in cases referred to our unit.

The results show that patients not already on dialysis responded uniformly well to the immunosuppressive drug regimen used, perhaps because of the consistent use of cyclophosphamide. In this situation, it was not possible to show additional benefit from the use of PE in terms of the proportion of patients improving, the degree of improvement or the subsequent need for dialysis. However, the mean percentage of circumferential crescents was less in the control group with creatinine > 500 μmol/liter than in the corresponding treatment group (Table 4); this could be obscuring a beneficial effect of PE. It is of interest that patients with MP and IRPGN responded equally as well as those with WG, which has previously been shown to respond to drug regimens including cyclophosphamide [33]. Other authors have recently reported that a similar "aggressive" approach to treatment leads to improved survival in patients with idiopathic RPGN and microscopic renal vasculitis when compared retrospectively with more conservatively treated cases [34–37].

A significant short-term benefit of PE in dialysis-dependent cases has been demonstrated for the first time, although numbers were small. There were several deaths within the first year, making longer-term comparison difficult. However, our results indicate a greater potential for recovery of renal function than that generally accepted [1, 32]. Patients with different clinicopathological diagnoses appeared to respond in a similar way. Interestingly, we have now observed short-term improvement in 13 of 16 ANCA positive dialysis-dependent patients with FNGN treated with PE, prednisolone and cyclophosphamide since the end of the trial (Mason PD et al, unpublished observations). This is in contrast to anti-GBM disease, in which dialysis-dependent cases rarely recover [5, 32, 38]. Although the proportion of crescents on renal biopsy may provide a guide to prognosis in untreated or less aggressively treated cases of FNGN [39], we have observed good responses to PE and drugs regardless of histological severity. It is acknowledged that the mean number of sclerosed glomeruli (as opposed to crescents) was slightly higher in the control group on dialysis, whereas the mean number of active crescents was higher in the treated group on dialysis (Table 4), but these differences were not statistically significant and there was wide individual variation. More detailed clinicopathological correlations in a larger group of patients are to be published separately, but the relationship between histological severity and clinical outcome was not good in aggressively treated cases [40].

The mechanism of action of PE in these patients remains unknown, although there are two major possibilities. First, it could act by removal of humoral inducers of glomerulonephritis such as immune complexes or autoantibodies. Circulating and/or deposited immune complexes are generally reported in between 1/3 and 2/3 of such cases [12, 41], but the inconsistency of these findings has led to doubts as to their clinical relevance. More recently, autoantibodies to a cytoplasmic constituent of neutrophils and monocytes (ANCA) have been demonstrated in a high proportion of patients with active WG [7, 42], MP [8] and IRPGN [15]. It is possible that these [43, 44], or related antibodies directed against endothelial cells [9–11], have a pathogenic role in systemic vasculitis. Second, PE could act by removal of inflammatory mediators responsible for tissue injury in glomerular disease, for example, complement components, fibrinogen or other coagulation factors [45, 46]. More specific forms of immunotherapy are needed to assess these possibilities.

This trial confirms that adequate oral immunosuppressive therapy (with or without PE) results in a favorable initial outcome in non-dialysis-dependent patients with FNGN, and suggests an additional benefit of PE in dialysis-dependent cases. Whether PE is more or less effective than high-dose intravenous methylprednisolone in this situation has not been examined, and this question could be addressed in further controlled studies. Long-term follow-up of these patients indicates that the initial improvement in renal function is generally maintained, usually with the use of low-dose maintenance immunosuppressive therapy, and strengthens the argument for an aggressive approach to the investigation and treatment of patients with severe glomerulonephritis.

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Reprint requests to Dr. C. D. Pusey, Renal Unit, Department of Medicine, Royal Postgraduate Medical School, Du Cane Road, London W12 ONN, England, United Kingdom.

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