

Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

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ABSTRACT

Systemic vasculitis associated with autoantibodies to neutrophil cytoplasmic antigens (ANCA) is the most frequent cause of rapidly progressive glomerulonephritis. Renal failure at presentation carries an increased risk for ESRD and death despite immunosuppressive therapy. This study investigated whether the addition of plasma exchange was more effective than intravenous methylprednisolone in the achievement of renal recovery in those who presented with a serum creatinine $>500 \mu\text{mol/L}$ (5.8 mg/dl). A total of 137 patients with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine $>500 \mu\text{mol/L}$ (5.8 mg/dl) were randomly assigned to receive seven plasma exchanges ($n = 70$) or 3000 mg of intravenous methylprednisolone ($n = 67$). Both groups received oral cyclophosphamide and oral prednisolone. The primary end point was dialysis independence at 3 mo. Secondary end points included renal and patient survival at 1 yr and severe adverse event rates. At 3 mo, 33 (49%) of 67 after intravenous methylprednisolone compared with 48 (69%) or 70 after plasma exchange were alive and independent of dialysis (95% confidence interval for the difference 18 to 35%; $P = 0.02$). As compared with intravenous methylprednisolone, plasma exchange was associated with a reduction in risk for progression to ESRD of 24% (95% confidence interval 6.1 to 41%), from 43 to 19%, at 12 mo. Patient survival and severe adverse event rates at 1 yr were 51 (76%) of 67 and 32 of 67 (48%) in the intravenous methylprednisolone group and 51 (73%) of 70 and 35 of (50%) 70 in the plasma exchange group, respectively. Plasma exchange increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure when compared with intravenous methylprednisolone. Patient survival and severe adverse event rates were similar in both groups.

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Wegener's granulomatosis and microscopic polyangiitis are primary systemic vasculitic disorders that are closely associated with circulating autoantibodies to neutrophil cytoplasmic antigens (ANCA) with specificity for proteinase 3 (PR3) or myeloperoxidase (MPO).^{1,2} Kidney involvement occurs in 70% of patients with histologic features of an intense, neutrophil-predominant inflammatory infiltrate; seg-

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mental glomerular necrosis reflecting a glomerular capillaritis; and intraglomerular monocyte proliferation contributing to a pauci-immune, focal and necrotizing, crescentic glomerulonephritis.³ Vasculitis accounts for 80% of cases of rapidly progressive glomerulonephritis, and progression to end-stage renal failure can be prevented by steroid and immunosuppressive therapy.^{4–7}

A role for ANCA in the pathogenesis of renal vasculitis is supported by the induction of neutrophil activation and superoxide release and neutrophil-mediated endothelial cytotoxicity by ANCA *in vitro*,⁸ by the induction of crescentic glomerulonephritis in animal studies by ANCA,^{9,10} and by the close association of ANCA with pauci-immune renal vasculitis.^{6,11,12}

Combination therapy with cyclophosphamide and prednisolone leads to remission in 80 to 90% of patients.¹² However, those who present with advanced renal failure have poorer outcomes, with only 50% surviving with independent renal function at 1 yr.⁵ The addition of intravenous methylprednisolone or plasma exchange has been advocated for those with severe vasculitic presentations.¹³ Plasma exchange was introduced for the removal of anti-glomerular basement membrane (GBM) antibodies in Goodpasture disease and used subsequently in crescentic glomerulonephritis without anti-GBM antibodies.^{14–16} A randomized trial in the latter group found improved outcomes with plasma exchange in those with severe renal failure at presentation.¹⁵ After the discovery of ANCA in the sera of patients with vasculitis and evidence supporting the pathogenicity of ANCA, a rationale has emerged for early plasma exchange to reduce levels of circulating ANCA and contribute to disease control in vasculitis.

The European Vasculitis Study Group has defined a “severe renal” subgroup as being patients who present with a serum creatinine $>500 \mu\text{mol/L}$ (5.8 mg/dl) attributable to active vasculitis.¹⁷ This study compared the addition of either intravenous methylprednisolone or plasma exchange with cyclophosphamide and oral prednisolone in severe renal vasculitis, with renal recovery as the primary outcome measure.

RESULTS

A total of 151 patients were screened between March 1995 and October 2002; nine were excluded for noneligibility (circulating anti-GBM antibodies, $n = 8$; and $>500 \text{ mg}$ intravenous methylprednisolone, $n = 1$), four declined further participation, and one center withdrew ($n = 1$; Figure 1). A total of 137 patients were randomly assigned to receive intravenous methylprednisolone ($n = 67$) or plasma exchange ($n = 70$). There were no significant differences in demographic, clinical, or laboratory features at the time of randomization (Table 1). All cases had histologic confirmation of the diagnosis. Subsequent histologic review of 102 (75%) of 137 diagnostic biopsies found no differences in the frequency or severity of histologic lesions between the two treatment groups (Table 2).

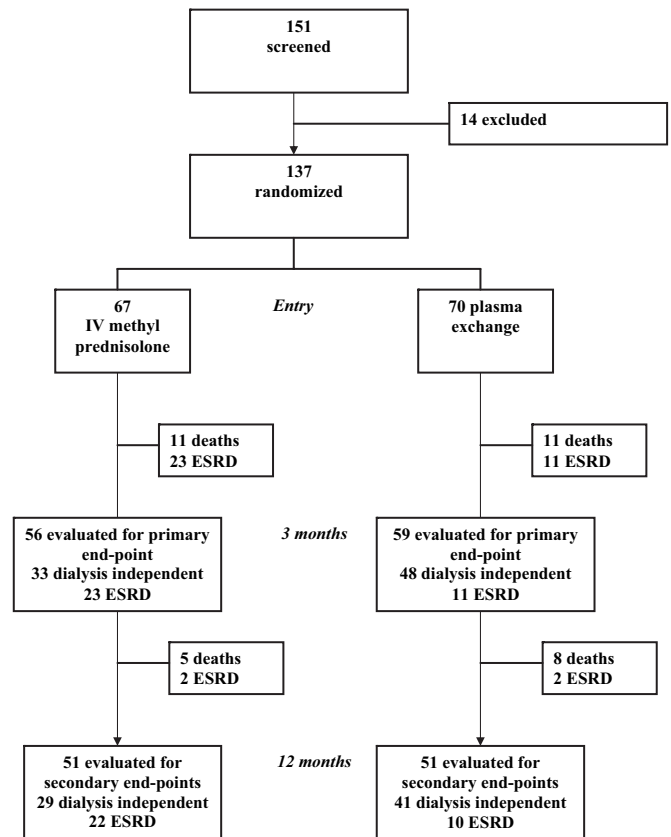


Figure 1. Enrollment, patient survival, and renal outcome during the trial.

Renal Recovery

By 3 mo, renal recovery had occurred in 33 (49%) of 67 of the intravenous methylprednisolone group and 48 (69%) of 70 of the plasma exchange group (95% confidence interval [CI] for the difference 18 to 35%; $P = 0.02$). Renal recovery had occurred by 6 wk in 66 and by 3 mo in 81 patients. At 12 mo, two from each group who had recovered renal function progressed to ESRD. Twenty-nine (43%) of 67 overall and 29 (57%) of 51 survivors in the intravenous methylprednisolone group and 41 (59%) of 70 overall and 41 (80%) of 51 survivors in the plasma exchange group remained alive and independent of dialysis (95% CI 4 to 40%; $P = 0.008$; Figure 2A). The hazard ratio for ESRD over 12 mo for plasma exchange *versus* intravenous methylprednisolone groups was 0.47 (95% CI 0.24 to 0.91; $P = 0.03$). The risk reduction for ESRD at 3 mo (23 [41%] of 56 for methylprednisolone *versus* 11 [19%] of 59 for plasma exchange) was 22% (95% CI 6.2 to 39). The risk reduction for ESRD at 12 mo (22 [43%] of 51 for methylprednisolone *versus* 10 [19%] of 51 for plasma exchange) was 24% (95% CI 6.1 to 41). The association of renal recovery and treatment with plasma exchange remained in the multivariate analysis ($P = 0.04$), but renal recovery was not significantly associated with stratification, age, diagnosis, or ANCA subtype.

Table 1. Baseline clinical and serologic characteristics of the patients with ANCA-associated systemic vasculitis and renal failure^a

Clinical and Laboratory Features at Entry	Intravenous Methylprednisolone (n = 67)	Plasma Exchange (n = 70)	Total (n = 137)	P
Age (yr; median [range])	66 (27 to 81)	67 (28 to 79)	66 (27 to 81)	0.93
Female gender (n [%])	24 (36)	29 (41)	53 (38.7)	0.50
Wegener's granulomatosis/microscopic polyangiitis (n [%])	24/43 (35.8/64.2)	18/52 (25.7/74.3)	42/95 (30.7/69.3)	0.20
Nonoliguric/dialysis requiring (n [%])	19/48 (28.4/71.6)	23/47 (32.9/67.1)	42/95 (30.7/69.3)	0.57
PR3-ANCA (n [%])	31 (46.3)	26 (37.1)	57 (42.6)	0.35
MPO-ANCA (n [%])	31 (46.3)	40 (57.1)	71 (51.9)	
ANCA negative (n [%])	3 (4.5)	4 (5.7)	7 (5.3)	
BVAS	21 (12 to 41)	21 (12 to 39)	21 (12 to 41)	0.69
Vasculitis Damage Index (median [range])	0 (0 to 4)	0 (0 to 7)	0 (0 to 7)	0.86
Creatinine (μmol/L; median [range])	718 (498 to 1566)	754 (500 to 1669)	735 (498 to 1669)	0.96
C-reactive protein (mg/L; median [range])	108 (2 to 264)	76 (7 to 281)	93 (2 to 281)	0.23
Erythrocyte sedimentation rate (mm/h; median [range])	84 (2 to 150)	94 (20 to 140)	89 (2 to 150)	0.34

^aANCA, autoantibodies to neutrophil cytoplasmic antigens; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; PR3, proteinase 3.

Table 2. Baseline histologic characteristics^a

Histologic Lesion	Intravenous Methylprednisolone (n = 49)	Plasma Exchange (n = 51)	Total Group (n = 100)
Glomerular			
% normal glomeruli	13.6 ± 18.2	12.1 ± 12.1	12.8 ± 15.3
% fibrinoid necrosis	28.9 ± 25.3	22.2 ± 24.9	25.5 ± 25.2
% crescents	59.2 ± 28.6	53.0 ± 28.9	56.0 ± 28.8
segmental	23.1 ± 23.4	28.9 ± 31.3	25.9 ± 27.3
circumferential	76.9 ± 44.3	71.1 ± 54.3	74.1 ± 49.5
cellular	90.4 ± 49.1	90.8 ± 57.2	90.6 ± 53.0
fibrous	9.6 ± 12.6	9.2 ± 18.0	9.4 ± 15.3
% global sclerosis	24.6 ± 26.9	28.2 ± 24.6	26.4 ± 25.7
Tubulointerstitial and vascular			
interstitial edema (0/1)	0.5 ± 0.5	0.5 ± 0.5	0.5 ± 0.5
interstitial infiltrates (0/1/2/3)	1.8 ± 0.7	1.8 ± 0.6	1.8 ± 0.7
neutrophilic (0/1/2)	0.7 ± 0.4	0.7 ± 0.5	0.7 ± 0.5
mononuclear cell (0/1/2)	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
eosinophilic (0/1/2)	0.4 ± 0.5	0.3 ± 0.5	0.4 ± 0.5
interstitial fibrosis (0/1/2)	1.2 ± 0.6	1.3 ± 0.6	1.2 ± 0.6
tubular casts (0/1)	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
tubular necrosis (0/1)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4
tubular atrophy (0/1/2)	1.1 ± 0.5	1.2 ± 0.6	1.1 ± 0.6
intraepithelial infiltrates (0/1)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4
arteriosclerosis (0/1)	0.8 ± 0.4	0.7 ± 0.4	0.8 ± 0.4

^aThe average distribution of the most characteristic glomerular, tubulointerstitial, and vascular lesions from 100 renal biopsies are described according to treatment group. This represents 75% of the 137 patients who were randomly assigned in this study. Glomerular lesions are expressed as a mean percentage ± SD of the total number of glomeruli per patient. All crescents were scored as either segmental or circumferential and as either cellular or fibrous, expressed as a percentage ± SD of the total number of crescents. Tubulointerstitial and vascular lesions were scored either in a dichotomous or in a semiquantitative manner. The numbers after every lesion indicate the possible scoring values.

Adverse Events

Patient survival at 3 and 12 mo was 56 (84%) of 67 and 51 (76%) of 67 in the intravenous methylprednisolone and 59 (84%) of 70 and 51 (73%) of 70 in the plasma exchange groups (log rank test *P* = 0.68; Figure 2B). The major causes of death were infection (*n* = 19), pulmonary hemorrhage (*n* = 6), and cardiovascular disease (*n* = 4). Patient survival was not significantly different between treatment groups and was not influenced by stratification, age, diagnosis, or ANCA subtype. In

those who survived beyond 6 wk, renal recovery was associated with increased patient survival between 6 wk and 12 mo (*P* = 0.005; Figure 2C).

A total of 244 adverse events were reported in 122 patients (Table 3). Severe or life-threatening events occurred in 32 (48%) of 67 of the intravenous methylprednisolone group and 35 (50%) of 70 of the plasma exchange group (*P* = 0.80). Leukopenia and infection were the most common adverse events. Although uncommon, severe thrombocytopenia and

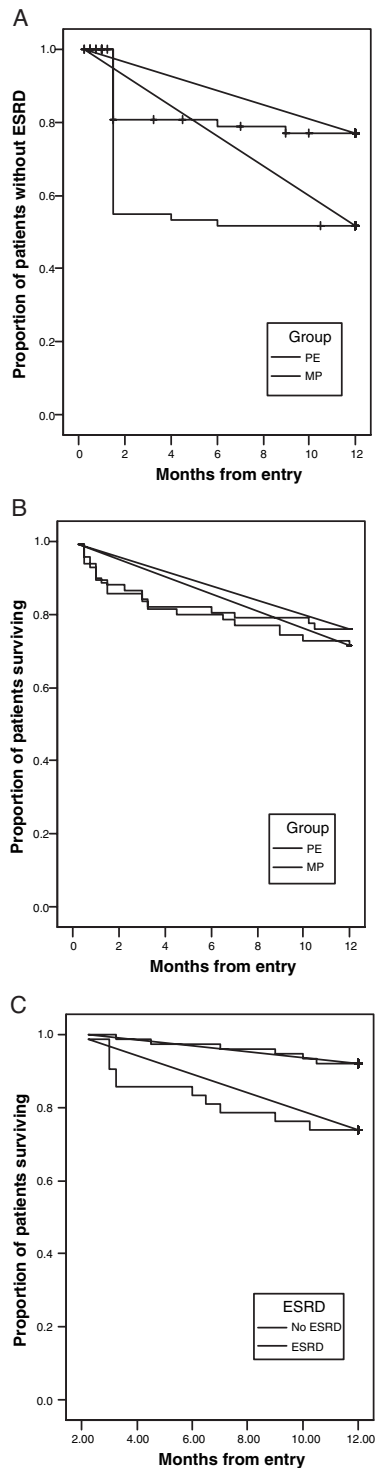


Figure 2. (A) Proportion of patients in each group without progression to ESRD. ESRD required at least 6 wk of dialysis dependence (intravenous methylprednisolone group [MP] versus plasma exchange group [PE] $P = 0.008$). (B) Proportion of patients in each group who survived during the trial (MP versus plasma exchange group $P = 0.68$). (C) For patients who were alive at 6 wk (119 of 137), the proportion of patients who subsequently survived according to whether they had recovered renal function or had reached end-stage renal failure at 6 wk ($P = 0.005$).

thrombosis were seen only in the plasma exchange group and may have been related to the procedure (Table 3).

Renal Function

There was no significant difference in the serum creatinine at 12 mo for those who recovered renal function between the two groups: $198 \mu\text{mol/L}$ (2.24 mg/dl; 95% CI 172 to 225) for the intravenous methylprednisolone group and $199 \mu\text{mol/L}$ (2.25 mg/dl; 95% CI 177 to 224) for the plasma exchange group ($P = 0.87$; Figure 3).

Birmingham Vasculitis Activity Scores

Scores for new or worse disease fell promptly with remission induction therapy and were similar between groups (Figure 4). Scores for persisting disease fell more slowly and remained at low levels during the trial without significant differences between groups.

Vasculitis Damage Index

By 6 and 12 mo, more damage accrued in the intravenous methylprednisolone group (mean 3.2 [95% CI 2.7 to 3.7] and 3.7 [95% CI 3.1 to 4.2]) than in the plasma exchange group (mean 2.3 [95% CI 1.7 to 3.0; $P = 0.005$] and 2.9 [95% CI 2.2 to 3.6; $P = 0.02$], respectively). In both groups, there were significant increases in damage between 0 and 6 mo ($P < 0.001$; Figure 5).

Short-Form 36

Physical and mental health measures all were $>30\%$ below the UK population norm at entry, with perceived role limitation due to physical problems at $>70\%$ below the norm. Physical health measures remained below control figures during the remission phase. Mental health measures improved to an average of 14% less than the control population at remission. Within-sample averages, for the whole cohort, showed a significant improvement with time throughout the trial ($P < 0.001$). No significant differences in Short-Form 36 (SF-36) scores were observed between groups.

DISCUSSION

This study found a higher rate of renal recovery and dialysis independence after plasma exchange than after the addition of intravenous methylprednisolone for patients with Wegener's granulomatosis or microscopic polyangiitis and a creatinine at diagnosis $>500 \mu\text{mol/L}$ (5.8 mg/dl). This effect was sustained to 12 mo from entry with only two from each group progressing to ESRD after initial recovery. The serum creatinine at 12 mo in those with renal recovery (mean $199 \mu\text{mol/L}$ [2.25 mg/dl]) is compatible with sustained renal independence in the absence of relapse of renal vasculitis.^{5,18} The degree of glomerulosclerosis and tubulointerstitial fibrosis is predictive of a poor renal outcome.¹⁹ Central review of diagnostic biopsies in this study found no differences in histologic variables between

Table 3. Adverse events according to type, severity (mild/moderate or severe/life threatening), and treatment group

Adverse Event	Study Groups				Total
	Intravenous Methylprednisolone		Plasma Exchange		
	Mild/Moderate	Severe/Life Threatening	Mild/Moderate	Severe/Life Threatening	
Leukopenia (at least 1 episode)	35	7	35	8	85
Recurrent leukopenia (>1 episode)	13	2	11	4	30
Infection	13	17	11	20	61
Thrombocytopenia	2	0	3	5	10
Allergy	4	0	6	0	10
Cardiovascular	2	3	1	3	9
Diabetes	3	2	2	1	8
Gastrointestinal	0	1	3	2	6
Bone fracture	0	2	1	2	5
Thrombosis	1	0	1	3	5
Hemorrhage	0	1	1	1	3
Alopecia	0	0	2	0	2
Vascular access complication	0	1	0	1	2
Other	1	3	2	2	8
Totals	74	39	79	52	244
No.(%) of patients with ≥1 event	59 (87)	32 (48)	63 (91)	35 (50)	122 (89)

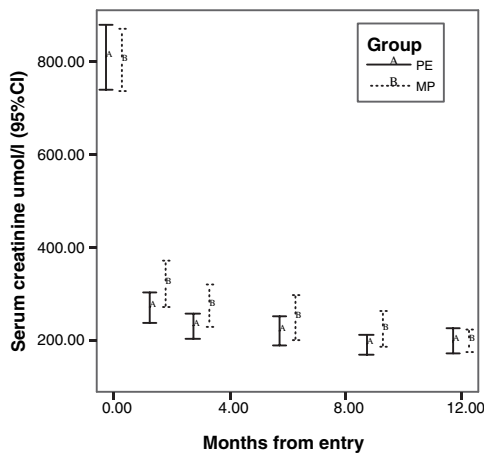


Figure 3. Sequential serum creatinine ($\mu\text{mol/L}$) for those who recovered renal function (mean; 95% confidence interval [CI]).

treatment groups, but because only 75% of biopsies were analyzed, an imbalance in the severity of fibrotic lesions cannot be entirely excluded.

The risk reduction of 24% for ESRD with plasma exchange is of clinical importance in view of the cost, morbidity, and mortality of end-stage renal failure, and the additional costs of plasma exchange are outweighed by these savings. The improvement in renal recovery rates with plasma exchange in the severe renal subgroup is consistent with our hypothesis that plasma exchange is most likely to be of benefit in those with the most severe disease. This study excluded patients who had been dialysis dependent for >2 wk because they were considered to have little chance of renal recovery.

Previous studies in rapidly progressive glomerulonephritis without anti-GBM antibodies have been small, have often included other diagnoses, and have failed to demonstrate a ben-

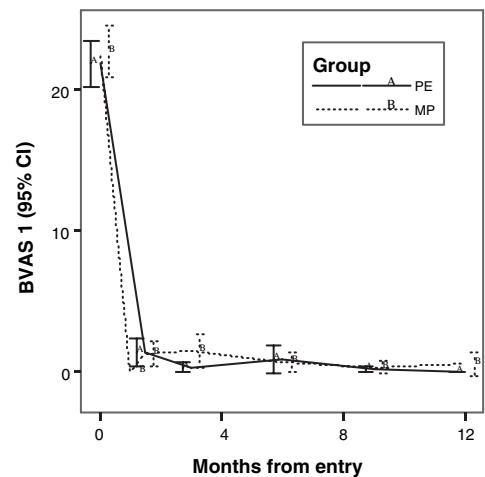


Figure 4. Sequential Birmingham Vasculitis Activity Score for new/worse disease (mean; 95% CI).

efit of plasma exchange except in subgroup analysis of those with advanced renal failure.^{15,16,20,21} The randomized, controlled trial of patients with systemic vasculitis reported by Pusey *et al.*¹⁵ showed a significant benefit in patients who were on dialysis at the start of treatment, although numbers were small. Two randomized studies in polyarteritis nodosa and Churg Strauss angiitis found no additional therapeutic efficacy of plasma exchange but did not have renal function as their primary end point.^{21,22} One randomized trial in Wegener's granulomatosis and three nonrandomized, controlled trials in ANCA-associated systemic vasculitis reported benefits of plasma exchange on renal outcome.^{23–26} Because this study focuses on a specific renal subgroup, its results are not in conflict with those showing negative results for plasma exchange and support the results of at least two previous randomized trials.^{15,24,25}

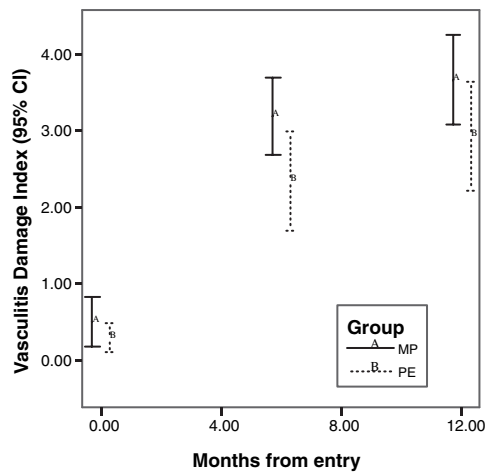


Figure 5. Sequential Vasculitis Damage Index scores (mean; 95% CI).

There was no difference in rates of adverse effects, infections, or mortality between treatment groups. Previous studies have demonstrated the safety of plasma exchange, and complications of vascular access are less relevant when this is also required for renal support.²⁷ The high rate of severe adverse events, 46%, was largely due to cytopenias and infections related to corticosteroids and cyclophosphamide. It was higher than in previous studies in patients with less severe renal function using similar regimens.^{5,12} This difference may in part be explained by the delayed clearance of cyclophosphamide and its metabolites in renal failure and by the age of patients in this study.²⁸

Mortality was 25.5% at 12 mo, considerably higher than in vasculitis studies without severe renal failure, with infection and lung hemorrhage being the major causes of death.^{12,29} Most deaths occurred during the first 3 mo, when corticosteroid dosages were highest and vasculitis was most active. A link among cyclophosphamide, neutropenia, sepsis, and death was previously shown, as was the independent role of steroid dosage on infective risk.⁵ However, after 3 mo, there was a higher mortality in those who had failed to recover renal function, confirming results from cohort studies.⁵ Thus, effective early therapy is imperative to avoid vasculitic death and maximize the chance of renal recovery. When compared with a study from this group of vasculitis with serum creatinine $<500 \mu\text{mol/L}$ (5.8 mg/dl), patients in this study were older (mean 64.3 versus 55.6 yr; $P < 0.0001$). They were also more likely to have a diagnosis of microscopic polyangiitis (69 versus 39%; $P < 0.0001$) and to be MPO-ANCA positive (52 versus 37%; $P = 0.003$).¹² Age has previously been shown to be associated with early mortality in renal vasculitis and may have accounted, in part, for the high mortality that was seen in this study.^{5,18} The contribution of drug toxicity to the mortality of severe renal vasculitis indicates that dosing of cyclophosphamide and corticosteroids in this patient group requires urgent consideration and emphasizes the need for safer agents.

Anti-MPO antibodies can cause glomerulonephritis and alveolar capillaritis in animal models, and ANCA have potent

effects on neutrophil activation, cytokine and enzyme release, leukocyte–endothelial interactions, and endothelial cytotoxicity in human *in vitro* systems.^{8,9,30–32} There is a rationale for the physical removal of ANCA by plasma exchange, whereas simultaneous corticosteroids and cyclophosphamide suppress inflammation and autoantibody production. Plasma exchange also removes other proinflammatory factors, including cytokines, complement, coagulation factors, soluble endothelial adhesion molecules and neutrophil enzymes, which may contribute to its effect.^{33,34} Sequential ANCA assays were not routinely performed in this study, and it is not known whether the dosage of plasma exchange should be titrated against the ANCA level, as has been advocated for anti-GBM disease.³⁵

Our study supports the use of plasma exchange in the treatment of ANCA-associated vasculitis that presents with renal failure. The role of intravenous methylprednisolone in addition to plasma exchange for this indication and the role of plasma exchange for other severe vasculitic manifestations, such as diffuse alveolar hemorrhage, requires further study.^{13,36,37}

CONCISE METHODS

Patients were recruited from 28 hospitals in nine European countries with local ethical approval after giving written informed consent. The study conformed to the 1964 Declaration of Helsinki and subsequent amendments.

Study Design

All patients received the same oral drug regimen of cyclophosphamide and prednisolone. At trial entry, patients were randomly assigned to receive, in addition, either intravenous methylprednisolone or plasma exchange. At 6 mo, cyclophosphamide was withdrawn and azathioprine was commenced. The study duration was 12 mo.

Eligibility Criteria

Inclusion required (1) a diagnosis of Wegener's granulomatosis or microscopic polyangiitis, using criteria adapted from the disease definitions of the Chapel Hill consensus conference^{1,12}; (2) biopsy-proven, pauci-immune, necrotizing, and/or crescentic glomerulonephritis, in the absence of other glomerulopathy; and (3) serum creatinine $>500 \mu\text{mol/L}$ (5.8 mg/dl). Exclusion criteria were (1) age <18 or >80 yr; (2) inadequate contraception in women of child-bearing age; (3) pregnancy; (4) previous malignancy; (5) hepatitis B antigenemia, anti-hepatitis C virus, or anti-HIV antibody; (6) other multisystem autoimmune disease; (7) circulating anti-GBM antibodies or linear IgG staining of the GBM on renal biopsy; (8) life-threatening nonrenal manifestations of vasculitis, including alveolar hemorrhage requiring mechanical ventilation within 24 h of admission; (9) dialysis for >2 wk before entry; (10) creatinine $>200 \mu\text{mol/L}$ (2.3 mg/dl) ≥ 1 yr before entry; (11) a second clearly defined cause of renal failure; (12) previous episode of biopsy-proven necrotizing and/or crescentic glomerulonephritis; (13) >2 wk of treatment with cyclophosphamide or azathioprine; (14) >500 mg of intravenous methylprednisolone; (15) plasma exchange within the preceding year; (16)

>3 mo of treatment with oral prednisolone; and (17) allergy to study medications.

Drug Regimens

Both groups received oral cyclophosphamide 2.5 mg/kg per d (2 mg/kg per d for age >60 yr), reduced to 1.5 mg/kg per d at 3 mo and stopped at 6 mo. Azathioprine 2 mg/kg per d was commenced at 6 mo. Oral prednisolone was tapered from 1 mg/kg per d at entry to 0.25 mg/kg per d by 10 wk, 15 mg/d at 3 mo and 10 mg/d from 5 to 12 mo. Prophylaxis against steroid-induced gastritis, fungal infection, and *Pneumocystis jirovecii* pneumonia was suggested but was not mandatory. The intravenous methylprednisolone group received 1000 mg/d intravenous methylprednisolone for three consecutive months, starting on the day of entry.

Plasma Exchange Procedure

Because plasma exchange protocols varied between participating centers, investigators were permitted to use their local procedure with respect to (1) plasma filtration or centrifugation, (2) vascular access, (3) anticoagulation, and (4) daily or alternate-day exchanges. The following aspects of the procedure were mandated in the protocol: (1) A total of seven plasma exchanges within 14 d of study entry, (2) a plasma exchange volume of 60 ml/kg on each occasion, and (3) volume replacement with 5% albumin. The use of fresh frozen plasma at the end of the procedure to replenish coagulation factors was recommended but not mandated for patients who were at risk for hemorrhage, for example after kidney biopsy.

Evaluations

Study assessments were performed after 0, 1.5, 3, 6, 9, and 12 mo. They included full blood count, erythrocyte sedimentation rate, C-reactive protein, alanine transaminase, serum creatinine, and glucose. Disease activity was measured by the Birmingham Vasculitis Activity Score.³⁸ Cumulative all-cause damage was scored in the Vasculitis Damage Index at 0, 6, and 12 mo.³⁹ The SF-36 questionnaire was performed at each assessment.⁴⁰ Adverse events were graded by 22 predefined criteria into mild, moderate, severe, or life threatening.

Renal Histology

A total of 102 (75%) renal biopsies from the 137 patients in the study were available for central review; in two, there was insufficient material for further analysis. Biopsies were taken at diagnosis and scored according to a previously standardized protocol.^{3,19} Briefly, each glomerulus was scored separately for the presence of fibrinoid necrosis, crescents (cellular/fibrous and segmental/circumferential), sclerosis (local, segmental, or global), periglomerular infiltrates, granulomatous reactions, and other lesions. Affected glomeruli were reported as the percentage of the total number of glomeruli in a biopsy. Most interstitial, tubular, and vascular lesions were scored dichotomously, except for interstitial infiltrates, type of cellular infiltrates (neutrophils, mononuclear cells, and eosinophils), interstitial fibrosis, and tubular atrophy, which were scored semiquantitatively. Each biopsy was evaluated by two observers. Discrepancies between observers were resolved by conference during central reviews to achieve a consensus for each biopsy. The average distribution of glomerular, tubu-

lointerstitial, and vascular lesions was evaluated for the total group of patients for whom histologic data were available. Comparisons between treatment groups were performed by independent-samples *t* test for glomerular lesions and by nonparametric analysis (Wilcoxon signed rank test) for tubulointerstitial and vascular lesions.

Outcome Measures

The primary efficacy measure was renal recovery at 3 mo defined by patient survival, dialysis independence, and serum creatinine <500 $\mu\text{mol/L}$ (5.8 mg/dl). Secondary end points included patient survival at 12 mo; ESRD, defined by dialysis requirement for at least 6 wk without subsequent renal recovery; serum creatinine in recovering patients at 12 mo; and adverse event rates.

Statistical Analyses

Randomization was performed centrally by permuted blocks of four stratified by country and by whether the patient was nonoliguric or likely to require dialysis within the next 48 h. Primary data were collected in record books and submitted for centralized computer entry. The data were validated against the record books before analysis (SPSS PC statistical package, version 9; SPSS, Chicago, IL) by two data managers who had sole access to the data.

The predicted renal recovery rate for the intravenous methylprednisolone group was 50%, and the study was designed to detect an increase in recovery rate in the plasma exchange group of >20% (*i.e.*, from 50% to at least 70%).⁴¹ Allowing for a 10% dropout, 150 patients were required to achieve a significance level of 0.05 (two sided) and power of 0.8.

The primary end point was analyzed according to the intention-to-treat principle with death being regarded as a failure to achieve renal recovery. Renal recovery rates at 3 mo were compared by the Pearson χ^2 test. Renal and patient survivals between groups were compared by the log-rank test. A Cox regression model was used to determine the hazard ratio for renal survival. The influence of treatment group, stratification (nonoliguric or dialysis requiring), age, diagnosis (Wegener's granulomatosis or microscopic polyangiitis), and ANCA subtype (PR3-ANCA or MPO-ANCA) on renal recovery and patient survival were assessed by Cox proportional hazards analysis. Patient survival after 6 wk was compared between patients who had recovered renal function and those who had not by log-rank test. Demographic details, adverse events, Birmingham Vasculitis Activity Score (area under the curve), serum creatinine, and Vasculitis Damage Index were compared between groups by Mann-Whitney *U* test or Pearson χ^2 test. SF-36 mean scores were calculated for each of the eight dimensions using the Likert method of summated ratings, and change in scores over time was compared between groups by repeated measures analysis. All tests of significance were two sided and were considered significant at the 0.05 level. No interim analyses were performed.

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DISCLOSURES

None.

REFERENCES

- Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG, et al.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 37: 187–192, 1994
- Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, Lesavre P, Ludemann J, Rasmussen N, Sinico RA, Wiik A, van der Woude FJ: Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int* 53: 743–753, 1998
- Hauer HA, Bajema IM, van Houwelingen HC, Ferrario F, Noel LH, Waldherr R, Jayne DR, Rasmussen N, Bruijn JA, Hagen EC; European Vasculitis Study Group (EUVAS): Renal histology in ANCA-associated vasculitis: Differences between diagnostic and serologic subgroups. *Kidney Int* 61: 80–89, 2002
- Jayne DR, Marshall PD, Jones SJ, Lockwood CM: Autoantibodies to GBM and neutrophil cytoplasm in rapidly progressive glomerulonephritis. *Kidney Int* 37: 965–970, 1990
- Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, Plaisance M, Pusey CD, Jayne DR; Pan-Thames Renal Research Group: Outcome of ANCA-associated renal vasculitis: A 5-year retrospective study. *Am J Kidney Dis* 41: 776–784, 2003
- Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J: Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol* 9: 842–852, 1998
- Falk RJ, Nachman PH, Hogan SL, Jennette JC: ANCA glomerulonephritis and vasculitis: A Chapel Hill perspective. *Semin Nephrol* 20: 233–243, 2000
- Hewins P, Savage CO: ANCA and neutrophil biology. *Kidney Blood Press Res* 26: 221–225, 2003
- Xiao H, Heeringa P, Hu P, Liu Z, Zhao M, Aratani Y, Maeda N, Falk RJ, Jennette JC: Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest* 110: 955–963, 2002
- Brouwer E, Huitema MG, Klok PA, de Weerd H, Tervaert JW, Weening JJ, Kallenberg CG: Antimyeloperoxidase-associated proliferative glomerulonephritis: An animal model. *J Exp Med* 177: 905–914, 1993
- Boomsma MM, Stegeman CA, van der Leij MJ, Oost W, Hermans J, Kallenberg CG, Limburg PC, Tervaert JW: Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: A prospective study. *Arthritis Rheum* 43: 2025–2033, 2000
- Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, Ekstrand A, Gaskin G, Gregorini G, de Groot K, Gross W, Hagen EC, Mirapeix E, Pettersson E, Siegert C, Sinico A, Tesar V, Westman K, Pusey C; European Vasculitis Study Group: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 349: 36–44, 2003
- Bolton WK, Sturgill BC: Methylprednisolone therapy for acute crescentic rapidly progressive glomerulonephritis. *Am J Nephrol* 9: 368–375, 1989
- Lockwood CM, Rees AJ, Pearson TA, Evans DJ, Peters DK, Wilson CB: Immunosuppression and plasma-exchange in the treatment of Goodpasture's syndrome. *Lancet* 1: 711–715, 1976
- Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM: Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int* 40: 757–763, 1991
- Cole E, Cattaran D, Magil A, Greenwood C, Churchill D, Sutton D, Clark W, Morrin P, Posen G, Bernstein K, et al.: A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group. *Am J Kidney Dis* 20: 261–269, 1992
- Jayne DR, Rasmussen N: Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: Initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. *Mayo Clin Proc* 72: 737–747, 1997
- Slot MC, Tervaert JW, Franssen CF, Stegeman CA: Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 63: 670–677, 2003
- de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, Noel LH, Ferrario F, Waldherr R, Hagen EC, Bruijn JA, Bajema IM: Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol* 17: 2264–2274, 2006
- Glockner WM, Sieberth HG, Wichmann HE, Backes E, Bambauer R,

- Boesken WH, Bohle A, Daul A, Graben N, Keller F, et al.: Plasma exchange and immunosuppression in rapidly progressive glomerulonephritis: A controlled, multi-center study. *Clin Nephrol* 29: 1–8, 1988
21. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T, Leon A, Bussel A: Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. *Arthritis Rheum* 38: 1638–1645, 1995
 22. Guillevin L, Jarrousse B, Lok C, Lhote F, Jais JP, Le Thi Huong Du D, Bussel A: Longterm followup after treatment of polyarteritis nodosa and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa. *J Rheumatol* 18: 567–574, 1991
 23. Frasca GM, Soverini ML, Falaschini A, Tampieri E, Vangelista A, Stefani S: Plasma exchange treatment improves prognosis of antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis: A case-control study in 26 patients from a single center. *Ther Apher Dial* 7: 540–546, 2003
 24. Szpirt WRN: Plasma exchange and cyclosporin A in Wegener's granulomatosis. *Int J Artif Organs* 10: 501–505, 1996
 25. Aasarod K, Iversen BM, Hammerstrom J, Bostad L, Jorstad S: Clinical outcome of patients with Wegener's granulomatosis treated with plasma exchange. *Blood Purif* 20: 167–173, 2002
 26. Nakamura T, Matsuda T, Kawagoe Y, Ueda Y, Ebihara I, Koide H: Plasmapheresis with immunosuppressive therapy vs immunosuppressive therapy alone for rapidly progressive anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis. *Nephrol Dial Transplant* 19: 1935–1937, 2004
 27. Bussel A, Jais JP: Side effects and mortality associated with plasma exchange: A three year experience with a regional register. *Life Support Syst* 5: 353–358, 1987
 28. Haubitz M, Bohnenstengel F, Brunkhorst R, Schwab M, Hofmann U, Busse D: Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. *Kidney Int* 61: 1495–1501, 2002
 29. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, Gross WL, Luqmani R, Jayne DR: Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 52: 2461–2469, 2005
 30. Little MA, Smyth CL, Yadav R, Ambrose L, Cook HT, Nourshargh S, Pusey CD: Antineutrophil cytoplasm antibodies directed against myeloperoxidase augment leukocyte-microvascular interactions in vivo. *Blood* 106: 2050–2058, 2005
 31. Ewert BH, Jennette JC, Falk RJ: Anti-myeloperoxidase antibodies stimulate neutrophils to damage human endothelial cells. *Kidney Int* 41: 375–383, 1992
 32. Falk RJ, Terrell RS, Charles LA, Jennette JC: Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. *Proc Natl Acad Sci U S A* 87: 4115–4119, 1990
 33. Cameron JS, Gill D, Turner DR, Chantler C, Ogg CS, Vosnides G, Williams DG: Letter: Combined immunosuppression and anticoagulation in rapidly progressive glomerulonephritis. *Lancet* 2: 923–925, 1975
 34. Tesar V, Jelinkova E, Masek Z, Jirsa M Jr, Zabka J, Bartunkova J, Stejskalova A, Janatkova I, Zima T: Influence of plasma exchange on serum levels of cytokines and adhesion molecules in ANCA-positive renal vasculitis. *Blood Purif* 16: 72–80, 1998
 35. Levy JB, Turner AN, Rees AJ, Pusey CD: Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Ann Intern Med* 134: 1033–1042, 2001
 36. Gallagher H, Kwan JT, Jayne DR: Pulmonary renal syndrome: A 4-year, single-center experience. *Am J Kidney Dis* 39: 42–47, 2002
 37. Nguyen T, Martin MK, Indrikovs AJ: Plasmapheresis for diffuse alveolar hemorrhage in a patient with Wegener's granulomatosis: Case report and review of the literature. *J Clin Apher* 20: 230–234, 2005
 38. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, Savage C, Adu D: Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 87: 671–678, 1994
 39. Exley AR, Bacon PA, Luqmani RA, Kitis GD, Gordon C, Savage CO, Adu D: Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 40: 371–380, 1997
 40. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 30: 473–483, 1992
 41. Jayne D: Clinical management and treatment of vasculitis. *Springer Semin Immunopathol* 23: 267–286, 2001

See the related editorial, "Removing Antibody and Preserving Glomeruli in ANCA Small-Vessel Vasculitis," on pages 1987–1989.