Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener’s granulomatosis—a clinical randomized controlled trial

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Abstract

Background. The use of plasma exchange (PE) for induction treatment of anti-neutrophil cytoplasm autoantibody (ANCA)-associated vasculitis (AAV), including Wegener’s granulomatosis (WG), is still controversial. The use of PE in AAV is not commonly accepted in patients with a plasma creatinine <500 μmol/L (5.7 mg/dL) despite experimental support for involvement of ANCA in the pathogenesis of vasculitis.

Methods. In a single-centre study from a tertiary referral centre, 32 patients with ANCA-positive WG were treated with standard immunosuppressive therapy, prednisolone and cyclophosphamide (CYC). In addition, they were randomized to treatment with or without initial PE. After 3 months, they were further randomized in a Latin square design to continue CYC or to change to cyclosporine A (CyA) for 9 months. The renal follow-up was at least 5 years.

Results. Renal survival after 1, 3 and 12 months, and 5 years was significantly better in the PE groups. For all groups, the kidney/patient survival was 87.5%/93.7% at 1 year and 72%/56% at 5 years. All patients who were on dialysis when recruited were dialysis dependent 5 years later. There was no difference in morbidity or mortality between PE and control groups. Multivariate analysis demonstrated that PE improved renal survival (P<0.01) at initial plasma creatinine levels >250 μmol/L (2.85 mg/dL). Change from CYC to CyA did not influence rate of relapses or time to relapse.

Conclusions. PE is recommended for induction therapy in WG patients at creatinine levels >250 μmol/L (2.85 mg/dL), whereas previous randomized studies have limited PE to patients with creatinine >500 μmol/L (5.65 mg/dL).

Keywords: ANCA; cyclosporine A; plasma exchange; vasculitis; Wegener’s granulomatosis

Introduction

The use of plasma exchange (PE) for induction treatment of anti-neutrophil cytoplasm autoantibody (ANCA)-associated vasculitis (AAV), including Wegener’s granulomatosis (WG), is still controversial. The use of PE in AAV is not commonly accepted in patients with plasma creatinine <500 μmol/L (5.65 mg/dL) despite experimental support for involvement of ANCA in the pathogenesis of vasculitis. Pusey et al. described the beneficial effect of PE in 48 rapidly progressive glomerulonephritis (RPGN) patients with or without systemic vasculitis, where anti-glomerular basal membrane (GBM) was excluded, in a subgroup of 19 patients requiring haemodialysis (HD) [1]. Ten out of 11 PE patients became HD-independent, while only 3 out of 8 patients in the control group did. No effect on renal function was found in patients with lower plasma creatinine values. The results of this study were based on survivor data only, and a high mortality of 48% in PE group and 35% in controls was reported. Furthermore, no long-term outcome was given. In contrast, in anti-GBM-associated disease, PE is recommended before severe kidney dysfunction is present, and dialysis dependency is a relative contraindication for PE use. The MEPEX study published in 2007 compared seven PE sessions to three methylprednisolone pulses and showed better preservation of renal function in the PE group at 3 months [2]. However, a high mortality of 26% in the first 12 months was experienced. The corresponding Journal of American Society of Nephrology (JASN) editorial [3] again recommended ‘...that PE should be reserved for severe kidney dysfunction, as the complications of this therapy, particularly the high mortality of plasmapheresis and oral cyclophosphamide, should limit this therapy only to dialysis patients with severe disease’.

In the present study, we decided to compare the effects of PE versus no PE and of cyclosporin A (CYC) versus cyclosporine A (CyA) in a randomized controlled trial.
Plasma exchange in vasculitis (RCT) with a Latin square design. Patients were included even with mild azotaemia. This study is therefore the first RCT with long-term follow-up, which specifically addresses the question of PE use in patients with plasma creatinine <500 μmol/L (5.65 mg/dL). A new multi-centre PE RCT, PEXIVAS, is in preparation and will include the patients with a moderate renal failure [<50 mL/min estimated glomerular filtration rate (eGFR)]. This study has influenced the design of PEXIVAS. The results of PEXIVAS, however, cannot be expected earlier than 2018.

Materials and methods

From 31 March 1990 to 16 December 1995, all C/PR3-ANCA-positive WG patients admitted to the State University Hospital, Rigshospitalet, Copenhagen, Denmark—a national, tertiary referral centre—were informed about the present study, and 32 were included after having obtained informed consent. They were initially randomized by the minimization method to additional PE. Randomization parameters at inclusion are shown with corresponding weighting factors in Table 1. The three plasma creatinine parameters were only used for randomization purposes since the number of patients in each group was too small for statistical analysis. The Minimize computer program [4] allocated every new case to the group with the lowest total score. After 3 months, the patients were again randomized to either replace CYC with CyA or continue with CYC for the following 9 months. The program thus created 4 treatment groups with 8 patients in each with 16 getting additional PE (PE groups and reference groups, respectively) and 16 being changed to CyA (Figure 1). All patients were followed up for 5 years after the last patient was recruited.

Inclusion criteria

All 32 patients were diagnosed as having WG based on the presence of a minimum of two of the following three inclusion criteria: (i) clinical manifestations of WG as defined by Faucci [5] from at least two organ systems, (ii) histology-proven WG, and (iii) positive ‘C-ANCA/PR3-ANCA’ by indirect immunofluorescence (IIF) and ELISA. All patients fulfilled the American College of Rheumatology 1990 criteria for the classification of WG [6].

Histology

Renal biopsies were performed within 2 weeks from admission in all patients with elevated plasma creatinine levels or proteinuria. Findings of focal necrotizing and crescentic glomerulonephritis were considered confirmative of the diagnosis. In nasal biopsies, small vessel vasculitis and/or granulomas and/or giant cells were considered confirmative.

ANCA detection methods

For inclusion, the rapid qualitative PR3-ELISA kit from Wieslab, Lund, Sweden was used, and the result was verified by IIF and a quantitative PR3-ELISA, where the antigen was purified neutrophil azurophil granules or purified proteinase3 (PR3) (Statens Serum Institute, Copenhagen, Denmark). C-ANCA titres >20 (i.e. positive at higher dilutions than 1:20) and ELISA readings >10 U/mL were considered positive. For statistical analysis, IIF titres were used.

Immunosuppression

Immunosuppressive treatment consisted of the following:

(i) prednisolone (oral corticosteroid, OCS) 80 mg daily for 3 weeks tapered to 5 mg and stopped after 9 months (relapses were treated with OCS increase to 40 mg daily);
(ii) CYC 1.5 mg/kg = 100/150 mg daily for 3 or 12 months depending on randomization after 3 months; and
(iii) CyA 5 mg/kg daily for 9 months after 3 months depending on randomization (the dose of CyA was later maintained based on blood—CyA levels, and a trough level between 150 and 200 μmol/L was considered acceptable).

Table 1. Randomization parameters at inclusion, with corresponding weighting factors

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>1.) Man</td>
<td>1</td>
</tr>
<tr>
<td>2.) Woman</td>
<td>2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>1.) &gt;50 years</td>
<td>3</td>
</tr>
<tr>
<td>2.) &lt;50 years</td>
<td>3</td>
</tr>
<tr>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td>1.) +WG</td>
<td>3</td>
</tr>
<tr>
<td>2.) −WG</td>
<td>3</td>
</tr>
<tr>
<td>Lung infiltrates</td>
<td></td>
</tr>
<tr>
<td>1.) + on X-ray</td>
<td>3</td>
</tr>
<tr>
<td>2.) − on X-ray</td>
<td>3</td>
</tr>
<tr>
<td>C-ANCA</td>
<td></td>
</tr>
<tr>
<td>1.) ELISA &lt;50</td>
<td>3</td>
</tr>
<tr>
<td>2.) ELISA &gt;50</td>
<td>3</td>
</tr>
<tr>
<td>Kidney function (plasma creatinine)</td>
<td></td>
</tr>
<tr>
<td>1.) &lt;130 μmol/L</td>
<td>8</td>
</tr>
<tr>
<td>2.) 130–300 μmol/L</td>
<td></td>
</tr>
<tr>
<td>3.) &gt;300 μmol/L</td>
<td></td>
</tr>
</tbody>
</table>

In 18 cases with clinical activity after 12 months—where CYC was not continued due to expected cumulative toxicity—azathioprine (AZA) had been given in 16 cases and chlorambucil in 2 cases when AZA intolerability was observed. AZA and chlorambucil were in all cases discontinued when active signs of disease had been absent for more than 12 months.

Plasma exchange

PE treatment comprised six membrane separation sessions using Gambro F-1000 filters (Gambro, Lund, Sweden) every other day. At each session, 4 L of plasma was exchanged with 3% albumin in Ringer’s Lactate. If C-ANCA titres were >320 or PR3-ANCA >25 U/mL on ELISA after six sessions, an additional 3–6 sessions were performed.

Relapses

We defined relapses as presence of clinical symptoms of active disease (the BVAS score was not developed when this study was designed) and at least three of the following factors: a 2-fold increase in IIF C/PR3-ANCA titre (repeated for confirmation), a 20% increase in plasma creatinine, an increase in proteinuria, and an increase in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Renal remission and progression

‘Remission’ was defined as creatinine decrease >15% from inclusion (i.e. >250 μmol/L), and ‘progression’ as unchanged when plasma creatinine was 300 μmol/L or 15% increased with creatinine <300 μmol/L in the first 12 months after recruitment.

Statistical analyses

cGFR was calculated using the modified four-variable MDRD equation [7]. Chi-square test was used for categorical comparison of the groups and Student’s t-test for parametric variables. Dialysis patients were assigned an arbitrary creatinine clearance of 6 mL/min and an eGFR of 5 mL/min. Cox proportional hazards analysis was used for evaluation of predictors. The following end points were evaluated: death, dialysis, death or dialysis, relapses, and all events combined. Logarithmic transformation was performed where indicated. Differences in clinical outcomes were assessed using Kaplan–Meier survival and Cox proportional hazards analysis. ANCA titres were converted to a semi-logarithmic scale before statistical analysis: 0 = 1, 40 = 2, 80 = 3, 160 = 4, etc. The ANCA titres are obtained from IIF. A P-value of <0.05 was accepted as significant.

The relationship of treatment effect to initial plasma creatinine was investigated by dividing the material into two creatinine groups, <250 and >250 μmol/L, corresponding approximately to the median initial value.

Results

The patients in the four treatment groups were comparable with respect to age, sex, ANCA titres, biopsy findings, pul-
monary involvement and decreased kidney function determined by eGFR and plasma creatinine levels (Table 2). The mean age was 57 years (range 27–77). Seven of 16 patients in the PE groups and 6 patients in the reference groups had plasma creatinine levels >300 µmol/L. A total of 22 patients had elevated creatinine levels, similarly distributed in all four groups. On admission, six patients were HD-dependent; four of these were in the reference groups. The 21 patients with lung infiltrates were also equally represented in all four groups. Twenty-six patients had active ENT involvement. Three had mononeuritis multiplex with peroneus paresis, and seven had skin vasculitis ulcers. The diagnosis was histologically confirmed in eight by nasal biopsy and in 23 by renal biopsy, and the results of seven of the biopsies were available at randomization (Table 1). Eight of all biopsies contained granuloma.

Renal outcome (Table 3)

After 1 month, none of the PE patients was on HD or in renal progression, which was significantly better than in the reference groups, where six were in renal progression and five on HD (P<0.05—chi-square test with Yates' correction). In PE groups, six patients in the group with plasma creatinine >300 µmol/L experienced improved renal function, two of them to the normal plasma creatinine group and four to the group with plasma creatinine between 130 and 300 µmol/L.

In the reference groups, only one patient improved renal function, included into the plasma creatinine group between 130 and 300 µmol/L. At 3 months, before treatment change from CYC to CyA, none of the PE patients had severely elevated plasma creatinine levels compared with four of the reference patients, and none of them, compared with five in the reference groups, was in renal progression (P = 0.05—chi-square test with Yates' correction). After 12 months, high plasma creatinine values were not observed in the PE group, and no patient was on HD (data not shown). However, 18 patients were still on immunosuppressive therapy, and 5 patients, 2 in the PE groups and three in the reference groups, were not in remission. Three of the five patients had been changed to CyA.

Eight of 18 patients with sclerosis and fibrosis on renal biopsy experienced improved renal function (44%): one patient with plasma creatinine <130 µmol/L, one patient with plasma creatinine between 130 and 300 µmol/L, and six patients with plasma creatinine >300 µmol/L. Six of the eight patients were in the PE groups.

For data exploration, patients were divided into two subgroups, <250 (azotaemic) and >250 µmol/L (uraemic), at the start (Table 4). PE patients showed similar improvements in both groups at 1 month. The improvement in plasma creatinine in the uraemic subgroup was significant.
For the azotaemic subgroup, one PE and one non-PE patient developed end-stage renal disease (ESRD), while for the uraemic group, one PE and six non-PE patients developed ESRD (P<0.01, Kaplan–Meier analysis).

A group of patients with an initial creatinine of 240–520 µmol/L (n=10, 5 PE and 5 non-PE) showed a similar trend for beneficial effect of PE.

The influence of PE on plasma creatinine is shown in Figure 2 with significantly lower values in the PE groups (P<0.05 at 1 month and P<0.01 at 5 years). The eGFR was insignificantly higher (Figure 3). eGFR is correlated to creatinine, but is a different variable, being derived from plasma creatinine, age, race and sex in an exponential algorithm.

For all 32 patients had positive ANCA titres. Significantly lower ANCA titres were found in the PE groups after 1 month (P<0.02), but this difference disappeared from 3 months onwards (Figure 4).

In the CyA groups, 10 patients had 18 relapses compared with the CYC groups where 8 patients had 13 relapses (not significant). Nineteen relapses responded to an increase in OCS, five relapses in three patients responded to a change from CyA to CYC and two relapses responded to additional PE (five sessions), whereas five could not be brought into remission.

Table 2. Distribution of clinical parameters in the four treatment groups at randomization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>+PE, +CyA</td>
<td>+PE, -CyA</td>
<td>-PE, +CyA</td>
<td>-PE, -CyA</td>
<td>32 patients</td>
</tr>
<tr>
<td>Age</td>
<td>6&gt;50&gt;2</td>
<td>6&gt;50&gt;2</td>
<td>6&gt;50&gt;2</td>
<td>6&gt;50&gt;2</td>
<td>24&gt;50&gt;8</td>
</tr>
<tr>
<td>Lung infiltrates</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>High &gt;50/low &lt;50 ANCA titre</td>
<td>6/2</td>
<td>6/2</td>
<td>7/1</td>
<td>7/1</td>
<td>26/6</td>
</tr>
<tr>
<td>Plasma creatinine in µmol/L, median (range)</td>
<td>295 (70–500)</td>
<td>230 (70–930)</td>
<td>370 (70–830)</td>
<td>130 (80–740)</td>
<td>240 (70–930)</td>
</tr>
</tbody>
</table>

Table 3. Renal outcome correlated to PE treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1+2</th>
<th>Group 3+4</th>
<th>Total 16/16</th>
<th>Group 1+2</th>
<th>Group 3+4</th>
<th>Total 16/16</th>
<th>Group 1+2</th>
<th>Group 3+4</th>
<th>Total 16/16</th>
<th>Group 1+2</th>
<th>Group 3+4</th>
<th>Total 16/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>0</td>
<td>6*</td>
<td>6</td>
<td>1</td>
<td>7*</td>
<td>8</td>
<td>5</td>
<td>11</td>
<td>16</td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Remission</td>
<td>16</td>
<td>10</td>
<td>26</td>
<td>15</td>
<td>9</td>
<td>24</td>
<td>11</td>
<td>5</td>
<td>16</td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>0</td>
<td>5*</td>
<td>5</td>
<td>0</td>
<td>4*</td>
<td>4</td>
<td>2</td>
<td>7*</td>
<td>9</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Creatinine &lt;130 µmol/L</td>
<td>7 (+2 patients)</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>130–300 µmol/L</td>
<td>8 (+4 patients)</td>
<td>6 (+1 patient)</td>
<td>14</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;300 µmol/L</td>
<td>1 (~6 patients)</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>4*</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

NS = P>0.10.

Table 4. Sub-analysis of the results for patients with plasma creatinine >250 and <250 µmol/L

<table>
<thead>
<tr>
<th>Creatinine &lt;250 at start</th>
<th>Mean</th>
<th>Creatinine &gt;250 at start</th>
<th>Mean</th>
<th>Creatinine 240–520 at start</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PE</td>
<td>No PE</td>
<td>P</td>
<td>PE</td>
<td>No PE</td>
</tr>
<tr>
<td>Creatinine 0 month</td>
<td>120</td>
<td>130</td>
<td>NS</td>
<td>520</td>
<td>590</td>
</tr>
<tr>
<td>Log-ANCA 1 month</td>
<td>2.00</td>
<td>3.11</td>
<td>NS</td>
<td>2.25</td>
<td>3.57</td>
</tr>
<tr>
<td>eGFR 1 month</td>
<td>67.1</td>
<td>55.9</td>
<td>NS</td>
<td>31.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Creatinine 1 month</td>
<td>110</td>
<td>190</td>
<td>NS</td>
<td>310</td>
<td>550</td>
</tr>
<tr>
<td>Creatinine clearance 1 month</td>
<td>79.7</td>
<td>67.1</td>
<td>NS</td>
<td>28.0</td>
<td>14.6</td>
</tr>
</tbody>
</table>

(P<0.02). For the azotaemic subgroup, one PE and one non-PE patient developed end-stage renal disease (ESRD), while for the uraemic group, one PE and six non-PE patients developed ESRD (P<0.01, Kaplan–Meier analysis).

A group of patients with an initial creatinine of 240–520 µmol/L (n=10, 5 PE and 5 non-PE) showed a similar trend for beneficial effect of PE.

ANCA

All 32 patients had positive ANCA titres. Significantly lower ANCA titres were found in the PE groups after 1 month (P<0.02), but this difference disappeared from 3 months onwards (Figure 4).

Relapses

In the CyA groups, 10 patients had 18 relapses compared with the CYC groups where 8 patients had 13 relapses (not significant). Nineteen relapses responded to an increase in OCS, five relapses in three patients responded to a change from CyA to CYC and two relapses responded to additional PE (five sessions), whereas five could not be brought into remission.
remission. Seven of the relapses occurred in four patients with normal renal function, whereas the remaining 24 relapses occurred in 14 patients with abnormal renal function. Eighteen relapses were late (>1.5 years after inclusion), all in patients with continuing immunosuppressive treatment (AZA). There was no significant difference in relapse rate or time to first relapse between the PE groups and the reference groups (Table 5), or between CYC and CyA groups.
No difference in relapse rate was found between 15 and 30 months when immunosuppression in all patients was stopped.

**Predictors**

The following variables at inclusion had no predictive value: symptom duration >3 months before admission (median 7.5 months), WG on biopsy, lung infiltrates, high ANCA >160 at admittance and >0 at 1 month, ESR or CRP >50, and CyA therapy. In contrast, kidney involvement (creatinine levels, crescents >70%, oliguria, proteinuria >1 g/day and HD) all had a significant impact on final kidney function outcome or death. ANCA titres at inclusion were of no predictive value on final outcome, and eight patients with high ANCA titres on follow-up were in complete clinical remission. Crescents >70%, oliguria and proteinuria were predictive of relapses (Table 6).

**Final clinical outcome**

All patients were followed up for at least 5 years. Five of six patients, who were HD-dependent on inclusion (one in the PE groups and four in the reference groups), had ESRD at 1 year and at 5 years, whereas the one HD-dependent patient in the reference groups, who had recovered renal function at 1 year, was also HD-dependent at 5 years. In addition, another patient in the PE and reference groups, respectively, became HD-dependent at 5 years (in total, two in the PE groups and seven in the reference groups) (P = 0.03) (Figure 4). As mentioned before, the PE group patients had a statistically better final outcome (P<0.01) (Figure 2). There was no difference in mortality between the PE groups and the reference groups. None of the patients was on immunosuppression after 30 months, and the length of the immunosuppressive treatment was not different between the PE and reference groups.

For all patients, the kidney/patient survival was 87.5%/93.7% at 1 year and 72%/56% at 5 years, respectively. Ten of 14 deaths were related to WG (4 in the PE groups versus 6 in the reference groups). Four serious infections, equally divided, were observed during the first year of treatment. In addition, two septicaemias occurred in the reference groups.

**Discussion**

This paper supports the additional use of PE on top of CYC and OCS for induction of remission not only for WG patients in renal failure but also for patients with moderately decreased renal function. CyA use in maintenance of remission does not increase the rate of relapses. It is probable that PE has been more important for treatment success than maintenance immunosuppressive therapy since the difference between the two groups was marked mostly at 1 month. The possible pathogenicity of ANCA is supported both in animal models and in vitro [8]. Furthermore, two reports of a transplacental transfer case from one MPO-ANCA-positive mother to her newborn infant have been published [9,10]. Another recent report, however, questioned whether MPO-ANCA transfer is pathogenic [11]. Removal of ANCA antibodies, adhesion molecules and cytokines could therefore have a beneficial effect on treatment results. In addition, removal of activated complement factors in AAV by PE might be advantageous, as complement activation, particularly by the alternative pathway, is involved in animal models of AAV [12]. Recently, anti-plasminogen antibodies [13] and antibodies against lysosomal-associated membrane protein-2 (LAMP-2) [14] have been described in AAV, and may also be removed by PE together with other so-called complementary antibodies. Present recommendations for PE in vasculitis are, however, still limited to (i) severe renal

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**Table 6. Significant initial factors affecting prognosis**

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>Death</th>
<th>Death+HD</th>
<th>Relapse</th>
<th>Any event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70% crescents</td>
<td>20.6 (4.3–99.6)**</td>
<td>6.2 (1.7–23.2)*</td>
<td>8.5 (2.4–30.1)**</td>
<td>3.7 (2.1–6.8)*</td>
<td>2.9 (1.7–4.7)*</td>
</tr>
<tr>
<td>Oliguric (&lt;400 mL/day)</td>
<td>0.14 (0.03–0.71)**</td>
<td>0.24 (0.07–0.78)**</td>
<td>0.25 (0.08–0.75)**</td>
<td>0.26 (0.09–0.74)*</td>
<td>0.27 (0.16–0.47)*</td>
</tr>
<tr>
<td>Clearance &gt;40 mL/min</td>
<td>0.24 (0.06–0.95)*</td>
<td>0.27 (0.16–0.47)*</td>
<td>0.26 (0.09–0.74)*</td>
<td>0.26 (0.09–0.74)*</td>
<td>0.26 (0.09–0.74)*</td>
</tr>
<tr>
<td>Clearance &gt;20 mL/min</td>
<td>6.9 (1.3–35.0)**</td>
<td>6.1 (1.7–22.7)**</td>
<td>5.3 (1.6–17.4)**</td>
<td>3.7 (1.4–10.2)**</td>
<td>3.0 (1.3–7.3)*</td>
</tr>
</tbody>
</table>

Data are presented as odds ratios (confidence limits).

*P<0.05; **P<0.01; ***P<0.001.
disease with plasma creatinine >500 µmol/L (5.7 mg/dL),
(ii) dialysis dependency, (iii) pulmonary haemorrhage, and
(iv) life-threatening neurological and gastrointestinal symp-
toms. These PE recommendations are predominantly based
on trials performed before the ANCA era. In the first two ran-
domized controlled trials [15,16] in patients who were not on
dialysis, no advantage was found, as judged by plasma cre-
atinine and dialysis dependency. However, in these studies,
changes in treatment modality during the trial and small pa-

tient numbers may have influenced the results. Three other
studies [17–19] demonstrated better renal outcomes in sub-
group analyses of those presenting with severe disease. An-
other did not show any influence of PE on renal function,
possibly because the exchanged volume was lower than the
commonly accepted [20]. A single non-randomized case-control
study from a single centre showed better renal survival in 26
patients with both moderately and severely decreased renal function [21]. The MEPEX study [2], pub-

lished in 2007 and initiated in 1995, compared 137 AAV
patients who were randomized to either seven PE sessions
of 60 mg/kg within 14 days or three daily infusions of
1000 mg of methylprednisolone. The inclusion criteria
were limited to patients with a plasma creatinine
>500 µmol/L (5.65 mg/dL) and demonstrated PE superior-
ity to methylprednisolone pulse at 3 months, but did not
answer the question whether PE treatment is superior to
a reference group not treated by PE. All patients received
oral CYC and the same OCS regimen. Renal recovery oc-
curred in 69% of the PE group and 49% of the control
group. Risk of progression to ESRD was reduced by PE
by 24%. The study of histological biopsies in the same co-
hort [22] found PE to be a positive predictor for HD inde-
pendency. Acute and chronic tubulointerstitial lesions
negatively predicted the final GFR, whereas the number
of normal glomeruli was a positive GFR predictor. Our
23 kidney biopsies showed fibrosis and sclerosis as a sign
of chronic damage in >50% of patients. These patients
should be treated intensively as patients with no sign of
chronicity on biopsy, as 44% regained renal function in
this study, including 5/6 patients with high plasma creatin-
ine, who were treated by PE.

As previously mentioned, the JASN editorial, which ac-
accompanied the MEPEX results [3], recommended restrict-

ing PE to patients with advanced renal disease and HD
because of a high risk of morbidity and mortality related
to PE and CYC. However, PE is per se not a dangerous
procedure in experienced hands. The PE mortality in a
series of >15 000 treatments was found to be <0.05%
[23]. We used lower CYC dose compared to earlier RCT
(1.5 mg/kg/day). Furthermore, PE, as an addition to in-
duction therapy, allows a reduction of CYC dose. Since con-
cclusion of the trial, we have included PE as standard
therapy in all AAV patients admitted to our centre, com-

bined with lower oral CYC doses of 100 mg daily for pa-
ants aged <65 years or 50 mg daily for >65 years [24].
OCS is given unchanged at a dose of 1 mg/kg daily. Mor-

tality and renal function preservation results are compar-
able or better than presently reported from other centres.

Twelve months of immunosuppressive treatment was in-
sufficient in 18 of our 32 WG patients. CyA can replace
CYC after treatment induction or can be used as CYC ‘spar-
ing’ but only in patients with moderate clinical activity or
remission. Patients can be switched back to CYC if progres-
sion is observed. We decided to introduce CyA for mainten-
ance of remission as several case reports suggested a posi-
tive CyA treatment effect. The use of CyA in AAV is,
however, not commonly accepted. Only one paper reported
lower relapse frequency in AAV with CyA compared with
AZA [25]. We could not reproduce these findings, but CyA
was at least equal to CYC in the first 9 months of mainte-
nance therapy, as there was no difference in the relapses be-
tween the groups. Our decision to limit CYC induction


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References


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