Early plasma exchange improves outcome in PR3-ANCA-positive renal vasculitis

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ABSTRACT

Objective. *Plasma exchange (PE) has been shown to improve renal outcome in anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) and severe renal failure; however the effect of PE in AAV with moderate renal impairment is controversial.*

Methods. *A single-centre, retrospective one-year follow-up study, including patients with renal AAV and eGFR <60 ml/min/1.73 m^2. Since 2007, all patients with renal AAV and eGFR <60 ml/min/1.73 m^2 had PE in addition to induction therapy with cyclophosphamide and prednisolone. Patients admitted from 1999 to 2007 that did not receive PE served as controls. The primary outcome was the combination of death, end-stage renal disease, and relapses after one year.*

Results. *A significant reduction in the primary endpoint was observed following the addition of PE (25% vs. 43%, p=0.04). Furthermore, a greater improvement in renal function after one year was observed among surviving PE treated patients not on dialysis (ΔeGFR 36.1 vs. 19.7 ml/min, p=0.03). There was a significant reduction in serious adverse events in the PE treated group (4% vs. 30%, p=0.02) despite no differences in types and doses of induction immunosuppressive therapy. The advantageous effect of PE was related to the presence of anti-proteinase3 (PR3)-antibodies and also evident among patients with plasma creatinine less than 500 μM.*

Conclusions. *This study suggests the use of PE in addition to standard induction treatment with cyclophosphamide and glucocorticoids to patients with renal PR3-AAV and an estimated-GFR <60 ml/min/1.73m^2.*

Introduction

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is characterised by inflammation in small blood vessels. Kidney involvement includes the histologic features of a neutrophil-predominant inflammatory infiltrate with capillaritis, vasculitis and glomerular necrosis resulting in a pauci-immune, focal and necrotising crescentic glomerulonephritis (1). The AAV encompasses granulomatosis with polyangiitis (GPA, formerly Wegener´s granulomatosis), microscopic polyangiitis (MPA) and Churg-Strauss syndrome, the latter rarely affecting the kidneys. AAV is associated with autoantibodies to proteinase-3 (PR3) and myeloperoxidase (MPO). GPA is generally associated with PR3-ANCA and MPA with MPO-ANCA.

Combination therapy with cyclophosphamide (CYC) and glucocorticoids has improved survival and transformed AAV from rapidly fatal diseases to ones of chronic morbidity frequently with chronic kidney disease and reduced long-term survival (2-6). The extensive immunosuppressive treatment is associated with many serious adverse effects, such as infections, infertility and cancer (2). Today the one-year mortality rate is 10%, but 50% of these deaths are related to the treatment itself (7). In recent years, plasma exchange (PE) has been used as part of the induction therapy in severe renal vasculitis. The MEPEX study (8) showed that PE improved renal survival in patients with AAV and plasma-creatinine >500 μM (5.8 mg/dl) when compared to intravenous methylprednisolone. Furthermore, Szprit *et al.* (9) has recently demonstrated that supplementation with PE improved renal survival in patients with PR3-ANCA-positive vasculitis and plasma creatinine >250 μM. However, the potential benefits of PE in patients with plasma creatinine <500 μM remain controversial.

We conducted a single-centre, retrospective one-year follow-up study evaluating the effect of PE on all patients with biopsy-proven renal AAV and estimated-GFR (eGFR) <60 ml/

min/1.73 m^2 comparing this to controls not treated with PE.

Subjects and methods

Design

The study is a single-centre, retrospective follow-up study including patients with AAV and renal involvement admitted to the Department of Nephrology, Aarhus University Hospital Skejby from 1999 to October 2010. During the period all patient received standard induction therapy with oral CYC (2 mg/kg bodyweight (BW), adjusted for age and renal function), except one patient in the PE group receiving iv. pulse CYC (15 mg/kg BW), and prednisolone (1 mg/kg BW). Since the late 2007 all patients with an eGFR <60 ml/min/1.73 m^2 were offered PE in addition. The decision to add PE to the standard treatment was a consequence of the MEPEX study (8) and based on the conception that the pathophysiology and progressive nature of the disease was likely to be independent of GFR in patients with kidney involvement. Before 2007, PE was administered only to patients presenting with an eGFR <10 ml/min/1.73 m^2 or dialysis-dependent and/or haemoptysis at the discretion of the treating physician. Five patients administered PE before 2007 were included; one was dialysis-dependent, one had haemoptysis and three patients presented with both an eGFR <10 ml/min/1.73 m^2/ dialysis-dependence and haemoptysis. Some patients were additionally given iv. methylprednisolone (500 mg/day for no more than three days) at initiation of therapy. Inclusion criteria were: 1) age >18 years, 2) eGFR <60 ml/min/1,73 m^2, 3) positive PR3- or MPO-ANCA, 4) renal biopsy with pauci-immune crescentic and/or focal glomerular necrosis, and 5) and no contraindications to PE or standard immunosuppression. Patients in remission were switched from CYC to either azathioprine (AZA) or mycophenolate mofetil (MMF) at 3–9 months along with low dose prednisolone. Prednisolone was tapered over 3 to 9 months to a dose of 5–10 mg/day.

Plasma exchange

PE treatment comprised 5-7 sessions within 14 days. At each session, four liters of plasma were exchanged with either human albumin 5% or a combination of human albumin and fresh frozen plasma if patients were actively bleeding or were found to be at high risk of haemorrhage, *e.g.* very recent lung bleeding or recent kidney biopsy.

Table I. Baseline demographic, clinical, serological and additional treatment characteristics.

	+ PE group	– PE group	*p*-value
Age (year, median, range)	64 (40-86)	67 (22-83)	0.37
Female gender	19/25 (76%)	28/50 (56%)	0.13
Comorbidity			
Ischaemic heart disease	2/25 (8%)	3/50 (6%)	1.0
Peripheral atherosclerotic disease	0/25 (0%)	2/50 (4%)	0.55
Previous stroke	0/25 (0%)	3/50 (6%)	0.55
Atherosclerotic disease*	2/25 (8%)	7/50 (14%)	0.71
Hypertension	8/25 (32%)	20/50 (40%)	0.62
Smokers**	5/21 (24%)	2/38 (5%)	0.09
Respiratory disease	1/25 (4%)	2/50 (4%)	1.0
Diabetes (type 1 and 2)	1/25 (4%)	7/50 (14%)	0.26
Autoimmune diseases***	2/25 (8%)	6/50 (12%)	0.71
Previous cancer	1/25 (4%)	1/50 (2%)	1.0
Disease manifestations			
PR3-/MPO-ANCA	16/9	25/25	0.33
P-creatinine (µM) (median, range)	432 (114-1330)	326 (100-1937)	0.11
eGFR (ml/min/1.73 m^2; median, range)	12.2 (3.5-59.1)	15.8 (1.7-59.4)	0.24
P-creatinine <500 µM	15/25 (60%)	37/50 (74%)	0.29
Requiring dialysis at admission	5/25 (20%)	9/50 (18%)	1.0
Haemoptysis at admission	7/25 (28%)	6/50 (12%)	0.11
Treatment			
Methylprednisolone for induction	16/25 (64%)	31/50 (62%)	1.0
CYC, total dose (g, median, range)	8.0 (1.1-26.3)	7.4 (1.1-50.7)	0.63
Steroids, total dose (g, median, range)	5.7 (2.9-9.5)	5.5 (1.0-11.4)	0.89
Maintenance therapy, azathioprine^	18/24 (75%)	13/43 (30%)	**<0.001**
Maintenance therapy, mycophenylate mofetil^	1/24 (4%)	14/43 (33%)	**0.007**

*Ischaemic heart disease, peripheral atherosclerotic disease and/or previous stroke; **Smoking habits was not consistently reported in all patients; ***RA, Mb. Becterew, primary biliary sclerosis, autoimmune thrombocytopenia, type 1 DM; ^Patients who died before achieving remission are excluded.

Table II. Baseline histological characteristics.

	+ PE group	- PE group	*p*-value
Glomerular			
% Normal glomeruli	34.0 ± (23.6)	27.4 ± (22.4)	0.16
% Fibrinoid necrosis	25.2 ± (19.4)	19.6 ± (17.6)	0.38
% Crescents	34.6 ± (22.5)	34.5 ± (26.9)	0.97
% Fibrotic crescents	2.3 ± (5.5)	4.4 ± (9.3)	0.41
% Global sclerosis (mean, SD)	6.3 ± (7.9)	12.7 ± (14.8)	0.08
Tubulointerstitial			
Tubular necrosis (0/1/2)	0.8 ± (0.6)	1.1 ± (0.7)	0.16
Tubular atrophy (0/1/2)	1.0 ± (0.7)	0.9 ± (0.6)	0.81
Interstitial infiltrates (0/1/2/3) (mean, SD)	1.3 ± (0.8)	1.1 ± (0.5)	0.46
Histopathological class			
Focal class	8/24 (33%)	10/45 (22%)	0.39
Crescentic class	9/24 (38%)	13/45 (29%)	0.59
Mixed class	7/24 (29%)	22/45 (49%)	0.13
Sclerotic class	0/24	0/45	1.0

The average distribution of glomerular and tubulo-interstitiel characteristics and the proportions of histopathological classes according to treatment group 24/25 and 45/50 biopsies were available for re-evaluation in the PE group and non-PE group, respectively.

Data collection

Patients were identified by searching the hospitals local registry for the following diagnosis; microangiopathia thrombotica, Wegener's granulomatosis and necrotising vasculitis. A search for

all patients who had been administered plasma exchange was also performed.
Medical files were reviewed and relevant clinical and biologic data were recorded.
All renal biopsies were re-evaluated by a single pathologist unaware of the treatment protocol. The proportion of normal glomeruli and those affected by necrosis, crescents and sclerosis was evaluated. Tubular necrosis, tubular atrophy and interstitial infiltrates were scored semi quantitatively. Biopsy findings were also categorised into focal, crescentic, sclerotic or mixed glomerulonephritis according to the newly proposed histopathological classification system for renal AAV (10). It was possible to re-evaluate 70 of 75 biopsies. PR3- and MPO-ANCA were identified by ELISA-technique using human PR3 and MPO as antigens.
The study was approved by the Danish Data Registry.

Outcome
Patients were followed for one year or until death. The primary outcome was the combination of death, ESRD and relapse within the first year. Relapse was defined by the treating physician as flares of clinical symptoms and increase in ANCA titer, which required intensified immunosuppression. Secondary endpoints included death, ESRD, relapse, and change in renal function from admission to one year. Plasma samples were collected on the day before the initiation of treatment and 12 months after. The plasma creatinine concentration was determined by a certified laboratory. Estimated GFR was calculated using the modified four variables MDRD-equation (11). The incidences of adverse and serious adverse events were also analysed. Adverse events were defined as any event that could be directly attributed to the treatment or not explained otherwise. Severe or life-threatening events were defined as adverse events with the potential to be life- or organ-threatening. The total amounts of CYC and steroids were calculated.

Statistical analysis
Baseline characteristics, primary and secondary endpoints, evaluation of adverse events and amounts of CYC and steroids were compared between groups by Fisher's exact test for parametric variables and the Mann-Whitney test for non-parametric variables. Primary endpoint and the secondary endpoints of ESRD and relapse were also evaluated using Kaplan-Meier survival curves, log-rank (Mantel-Cox) test and calculation of hazard ratios. The change in eGFR from admission to one year was calculated for each patient and differences between groups were evaluated using the Mann-Whitney test. All statistical analysis was performed using GraphPad Prism 5.

Table III. Clinical outcome according to treatment group and ANCA subtype.

		+ PE group	– PE group	*p*-value
Death/ESRD/relapses	All patients	5/25 (20%)	23/50 (46%)	**0.04**
	PR3-ANCA +	2/16 (13%)	15/25 (60%)	**0.004**
	MPO-ANCA +	3/9 (33%)	8/25 (32%)	1.0
Patients with p-creatinine <500 μM	All patients	1/15 (7%)	16/37 (43%)	**0.01**
	PR3-ANCA +	1/10 (10%)	11/20 (55%)	**0.02**
	MPO-ANCA +	0/5 (0%)	5/17 (29%)	0.29
Death	All patients	1/25 (4%)	8/50 (16%)	0.26
	PR3-ANCA +	0/16 (0%)	4/25 (16%)	0.14
	MPO-ANCA +	1/9 (11%)	4/25 (16%)	1.0
Patients with p-creatinine <500 μM	All patients	0/15 (0%)	5/37 (14%)	0.30
	PR3-ANCA +	0/10 (0%)	2/20 (10%)	0.54
	MPO-ANCA +	0/5 (0%)	3/17 (18%)	1.0
ESRD	All patients	4/25 (16%)	10/50 (20%)	0.76
	PR3-ANCA +	1/16 (6%)	5/25 (20%)	0.38
	MPO-ANCA +	3/9 (33%)	5/25 (20%)	0.65
Patients with p-creatinine <500 μM	All patients	1/15 (7%)	3/37 (8%)	1.0
	PR3-ANCA +	1/10 (10%)	1/20 (5%)	1.0
	MPO-ANCA +	0/5 (0%)	2/17 (12%)	1.0
Relapses	All patients	1/25 (4%)	8/50 (16%)	0.26
	PR3-ANCA +	1/16 (6%)	8/25 (32%)	0.07
	MPO-ANCA +	0/9 (0%)	0/25 (0%)	1.0
Patients with p-creatinine <500 μM	All patients	0/15 (0%)	7/37 (19%)	0.09
	PR3-ANCA +	0/10 (0%)	7/20 (35%)	0.06
	MPO-ANCA +	0/5 (0%)	0/17 (0%)	1.0
Adverse events (n, total pt)	All patients	65 (25)	141 (50)	0.79
	PR3-ANCA +	34 (16)	63 (25)	0.97
	MPO-ANCA +	30 (9)	78 (25)	0.47
>3 adverse events	All patients	7/25 (28%)	13/50 (26%)	1.0
	PR3-ANCA +	3/16 (19%)	6/25 (24%)	1.0
	MPO-ANCA +	4/9 (44%)	7/25 (28%)	0.43
≥1 serious event	All patients	1/25 (4%)	15/50 (30%)	**0.02**
	PR3-ANCA +	1/16 (6%)	10/25 (40%)	**0.03**
	MPO-ANCA +	0/9 (0%)	5/25 (20%)	0.29

Results

Study population
Seventy-five patients were included. Twenty-five patients received PE as supplement to the standard induction therapy with CYC and glucocorticoids while 50 patients were treated with the standard induction therapy alone. Forty-six patients received maintenance treatment with AZA or MMF, 9 patients died before they achieved remission, and 17 were maintained on low dose steroids alone (four in the PE-group and 13 in the non-PE group, p=0.39) because of either ESRD (n=12) or severe adverse events from immunosuppression (n=5). Three patients were kept on low dose CYC as maintenance therapy (all in the non-PE group). More patients in the PE group received AZA and less received MMF compared to patients in the non-PE group (Table I). All patients received the intended

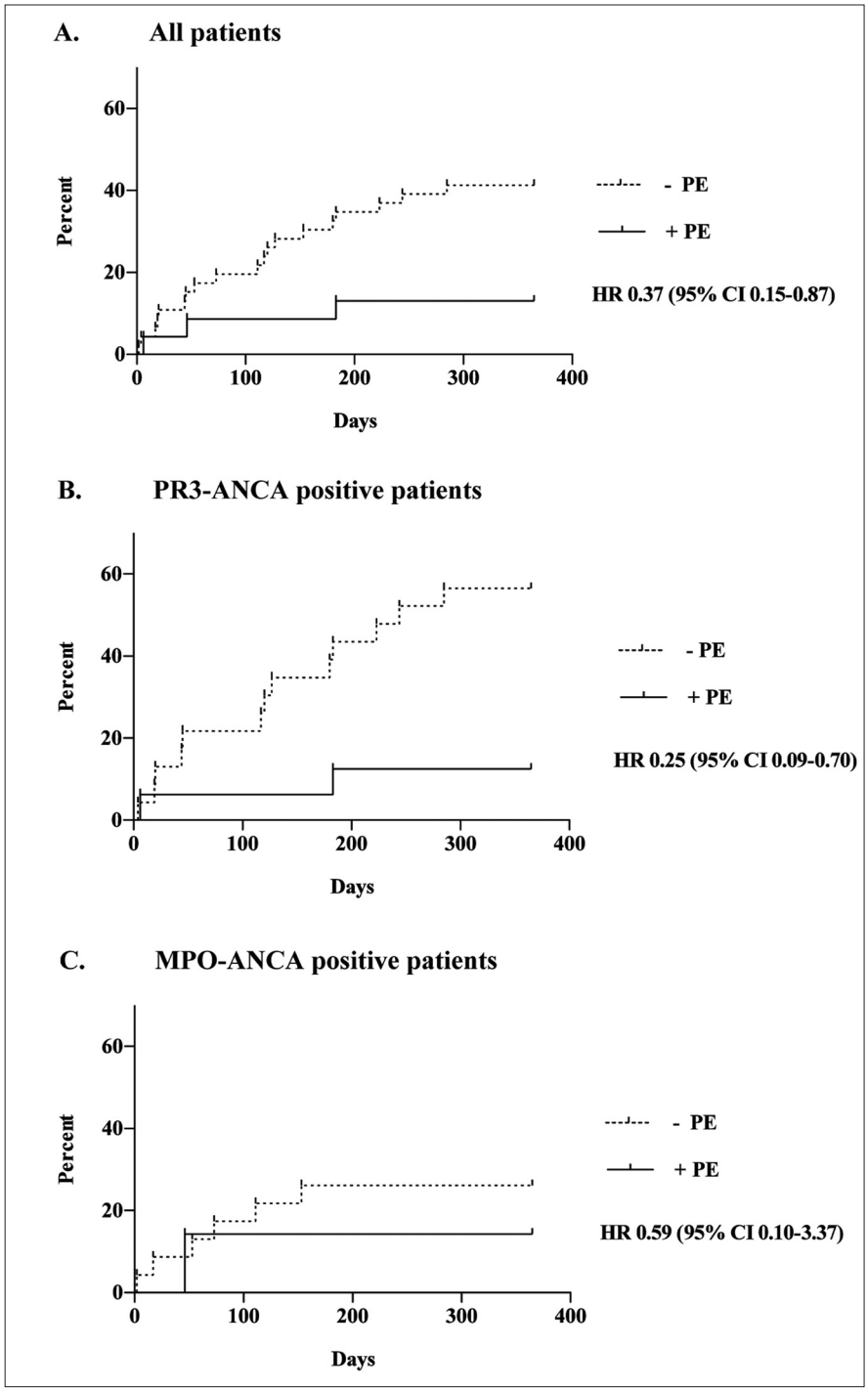

Fig. 1. The primary outcome. The risk of death, ESRD and relapse according to treatment group all patients (A) and by ANCA subtype (B and C).

number of PE sessions. Seventy-six percent (19/25) of the patients received seven PE sessions, 20% (5/25) six and 4% (1/25) five sessions.

No differences were observed between treatment groups in baseline characteristics or histological findings (Tables I and II). There were significantly more sclerotic glomeruli and tubular necrosis and atrophy in kidneys from MPO-ANCA positive patients compared to PR3-ANCA positive patients (data not shown).

There was no difference in the total amounts of steroids or CYC administered between the PE and non-PE groups (Table I), or in relation to ANCA subtype (data not shown).

Outcome

– Primary endpoint (death, ESRD and relapse)

Twenty percent of the patients in the PE-group reached the primary endpoint compared to 46% of the patients in the non-PE group (p=0.04, Table III). Among the PR3-ANCA positive patients, only 13% of the patients receiving PE reached the primary endpoint versus 60% in the non-PE group (p=0.004). In contrast, no significant difference was observed among the MPO-ANCA positive patients (Table III). The hazard ratio (HR) for the combined primary endpoint for PE versus non-PE was 0.37 (95% CI 0.15-0.87) for the whole group and 0.25 (0.09-0.70) and 0.59 (0.10-3.37) for PR3-ANCA and MPO-ANCA positive patients, respectively (Fig. 1). Subgroup analysis showed that PE also was beneficial in patients with plasma creatinine less than 500 μM, but only in patients with PR3-AAV (Table III); the HR for PE *vs*. non-PE was 0.29 (0.11-0.82) in the total group of patients, and 0.28 (0.09-0.90) and 0.26 (0.03-1.98) among the PR3-ANCA positive and the MPO-ANCA positive patients, respectively.

Mortality

No difference was observed in the mortality between the PE and the non-PE group, neither according to ANCA subtype nor in patients with plasma creatinine less than 500 μM (Table III). Deaths were attributable to uncontrolled disease, severe adverse events of the treatment, especially serious infections, and cancer (Table IVA).

Renal outcome

There was no significant difference in the number of patients, who developed ESRD within the first year (Table III and Fig. 2A); however, among surviving patients not on dialysis, renal function improved more in the patients of the PE-group compared to the non-PE group (36.1 *vs*. 19.7 ml/min, p=0.03, Fig. 4A). The benefit of PE was also seen in the group of patients with plasma creatinine less than 500 μM (ΔeGFR 33.8 *vs*. 11.7 ml/min, p=0.03) (Table III, Fig. 4B).

Table IV. Causes of death and adverse events according to treatment group.

A. *Causes of death*	+ PE group, number of deaths	– PE group, number of deaths
Pneumonia, n=1	Uncontrolled AAV-disease, n=1 Gastrointestinal bleeding, n=2 Multiorgan failure, n=1 Sepsis, n=1 Pneumonia, n=1 Thyroid cancer, n=1 Unknown, n=1	
B. *Adverse events*	+ PE group, number of events	– PE group, number of events
Severe adverse events (SAE)	Pneumocystis jiroveci pneumonia, n=1	Pneumocystis jiroveci pneumonia, n=3 CMV disease/pneumonia, n=4 Systemic/severe candida albicans infection, n=3 Other serious infectious illnesses, n=3 Malignity, n=2 Lung embolus, n=1 Severe hepatitis, n=1 Severe gastrointestinal bleeding, n=1 Perforation of the colon, n=1 Avascular necrosis of the femoral head, n=1 Severe, acute pancreatitis, n=1 Osteoporotic fracture of the spine, n=1
Adverse events (AE)	Haematological abnormalities*, n=31 Infectious, n=32 Alopecia, n=1	Haematological abnormalities*, n=59 Infectious, n=50 Deep venous thrombosis, n=4 Alopecia, n=3 Diabetes, n=2 Duodenal ulcer, n=1 Osteoporosis, n=1

*Leukopenia, anaemia, or thrombocytopenia.

When analysing by ANCA-type, PR3-ANCA positive patients not on dialysis at one year revealed a significantly greater increase in eGFR in the PE group compared to the non-PE group (46.8 *vs*. 24.5 ml/min, p=0.03, Fig. 4A). The effect of plasma exchange on the number of PR3-ANCA positive patients developing ESRD was not significant (Table III and Fig. 2). Among the MPO-ANCA positive patients, there was no significant difference between groups neither in the change in renal function (Fig. 4), nor in the incidence of ESRD (Table III, Fig. 2).

Relapses

The risk of relapse within one year was significantly reduced in the patients receiving PE compared to the patients only receiving standard therapy (HR 0.32, 95% CI 0.13-0.82, Fig. 3A).

All relapses were observed in the PR3-ANCA positive group of patients. Only six percent (1/16) of the PR3-ANCA positive patients who received PE developed a relapse in contrast to 32% (8/25) of the patients in the non-PE group (HR 0.22, 95% CI 0.07-0.64, Fig 3B). The effect of PE was also seen in the group of PR3-ANCA positive patients with plasma creatinine less than 500 μM. In this subgroup none of ten patients who received PE relapsed compared to 35% (7/20) in the non-PE group (HR 0.19, 95% CI 0.05-0.67).

There was no difference in the incidence of a relapse between the patients that had been switched to MMF (13%, 2/15) or AZA (13%, 4/31).

Adverse events

A total of 65 adverse events (AE) were recorded in the PE group (2.6 AE/patient), compared to 141 in the non-PE group (2.8 AE/patient) (p=0.79, Tables III and IVB). There was no difference between the groups in the number of patients experiencing more than three adverse events (24% *vs*. 26%, p=1.0), but the proportion of patients developing a severe or life-threatening event were significantly lower in the PE group compared to the non-PE group (4% *vs*. 30%, p=0.02, Table III and IV). The beneficial effect of PE was observed in the PR3-ANCA positive group where 6% compared to 40% in the non-PE group experienced a serious life-threatening event (p=0.03). Among MPO-positive patients none of the PE-treated experienced such an event compared to 20% of the non-PE patients, but the difference was not significant (p=0.29). There was no difference between treatment groups among patients with a plasma creatinine less than 500 μM (data not shown). None of the adverse effects in the PE group were directly related to the PE procedure.

Discussion

This non-randomised study shows a significant reduction in the combined endpoint of death, ESRD and relapses after one year following the addition of PE to standard induction immunosuppression in renal AAV. Furthermore, a better recovery of renal function estimated by eGFR after one year was observed among surviving patients not on dialysis. The study also shows a significant reduction in serious adverse events in the PE treated group despite no differences in the type or amount of induction immunosuppressive therapy. Finally, it demonstrates that the advantageous effect of PE is associated to positive PR3-ANCA and also evident in patients with plasma creatinine less than 500 μM.

The use of PE for crescentic glomerulonephritis was proposed already in the 1970 (12), but it was not until the MEPEX study (8) in 2007 that PE was generally established as a treatment modality in renal AAV with severe renal failure. In the MEPEX study 137 patients with AAV and plasma-creatinine >500 μM was randomised to adjunctive therapy of either PE or intravenous methylprednisolone. The renal outcome by 3 and 12 months was better in patients receiving PE, but this effect could not be demonstrated at longer follow-up (13). Outcome by 12 months was

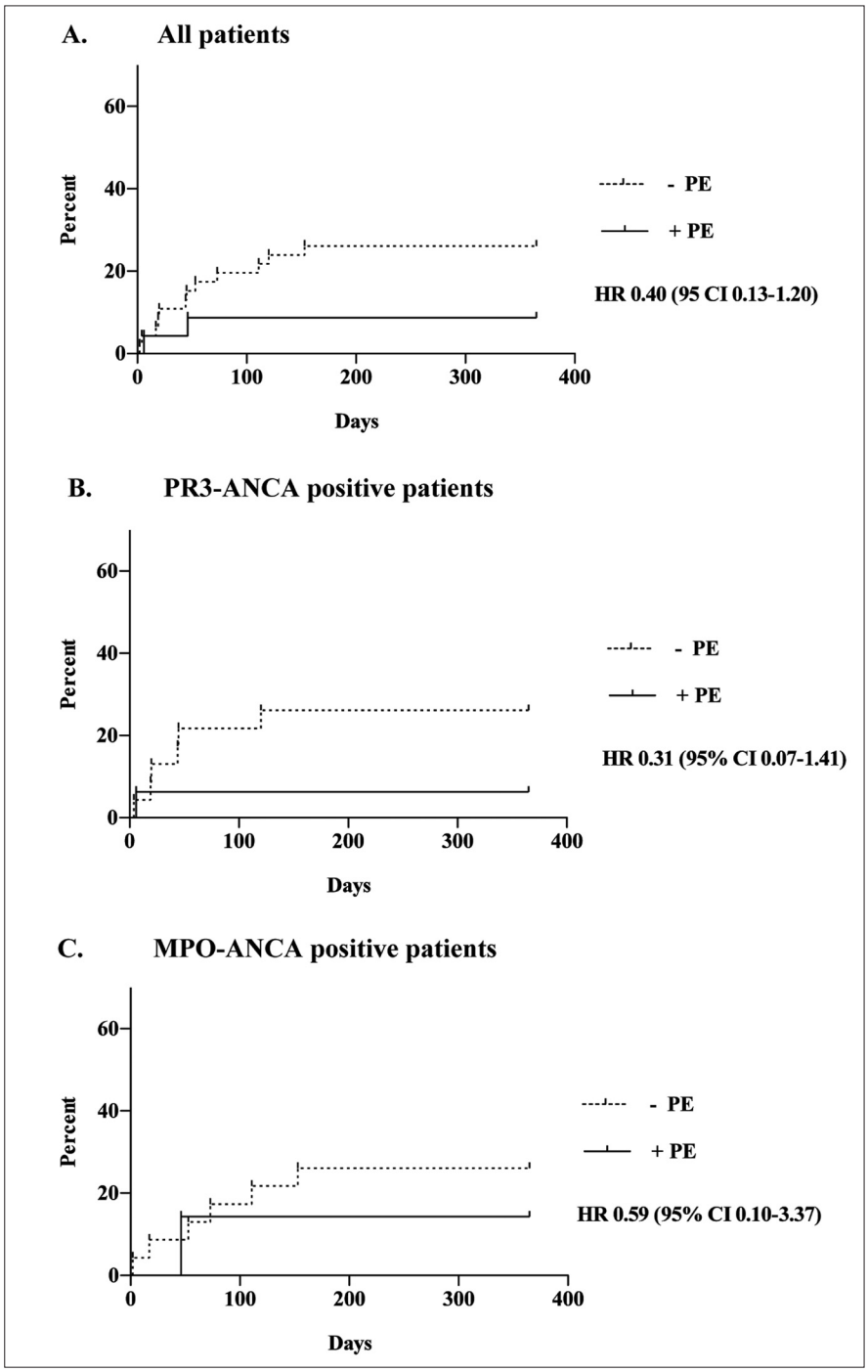

Fig. 2. The risk of ESRD according to treatment group in all patients (**A**) and by ANCA subtype (**B** and **C**).

not related to ANCA subtype. Similarly, Szpirt *et al*. (9) recently showed that PE in addition to standard treatment with oral CYC and prednisolone in patients with PR3-positive, renal vasculitis and moderate kidney impairment (plasma creatinine >250 μM) significantly improved renal survival after 1, 3 and 12 months. Eight other randomised controlled trials (reviewed in 14) have failed to recognise clear benefits from PE in the treatment of renal AAV, but all these studies were small, and did not, except one (15), differentiate between patients with PR3- and MPO-ANCA positive vasculitis. Furthermore, renal function was severely impaired with mean plasma creatinine >315 μM.

The pathogenesis of AAV is complex. ANCA is believed to play a pathogenic role by itself. ANCA binds to PR3 or MPO on cytokine-primed neutrophils leading to increased transmigration of neutrophils, endothelial cell injury and vasculitis (16-19). Adoptive transfer of anti-MPO-IgG or immunisation with MPO can induce crescentic glomerulonephritis in mice and rats (20-22). However, accumulating data indicates that the two diseases are different in clinical presentation and pathogenesis with T-cells in a central role, especially in PR3-ANCA positive AAV. A recent study showed association of anti-PR3 positive AAV with HLA-DR15, an association not seen in MPO-ANCA positive disease (23), which indicates a major role for T cells in the pathogenesis of anti-PR3 positive AAV. Furthermore, elevated levels of autoantigene-specific Th17 cells and Th17 related cytokines IL-17 and IL-23 have been demonstrated in peripheral blood of GPA patients (24). However, a T-cell mediated immune response does not exclude a positive effect of PE. The immune system interacts through cytokines and other soluble, signaling molecules. PE removes these molecules in conjunction with the neutrophil-activating antibodies as well as complement, adhesion molecules and components of the inert immune system (25). One could speculate that PE contributes in terminating the ongoing disease process and lower the inflammatory burden on the organs including the kidneys. In such setting, a positive response of PE would require early intervention. The biopsies of the MPO-ANCA positive patients revealed more advanced disease with more sclerotic glomeruli and tubular atrophy (data not shown). This more advanced disease stage in the MPO-ANCA positive patients, may at least to some extent, explain why the positive effect of PE was only seen in PR3-ANCA positive patients.

The adverse effects of PE are generally few when used by experienced hands, but PE is not entirely harmless, though, and the potential risk of the treatment should be considered. The World Apheresis Registry 2007 reported adverse events in 5.7% of 838 patients receiving PE, but no related deaths (26). In our study we did not observe

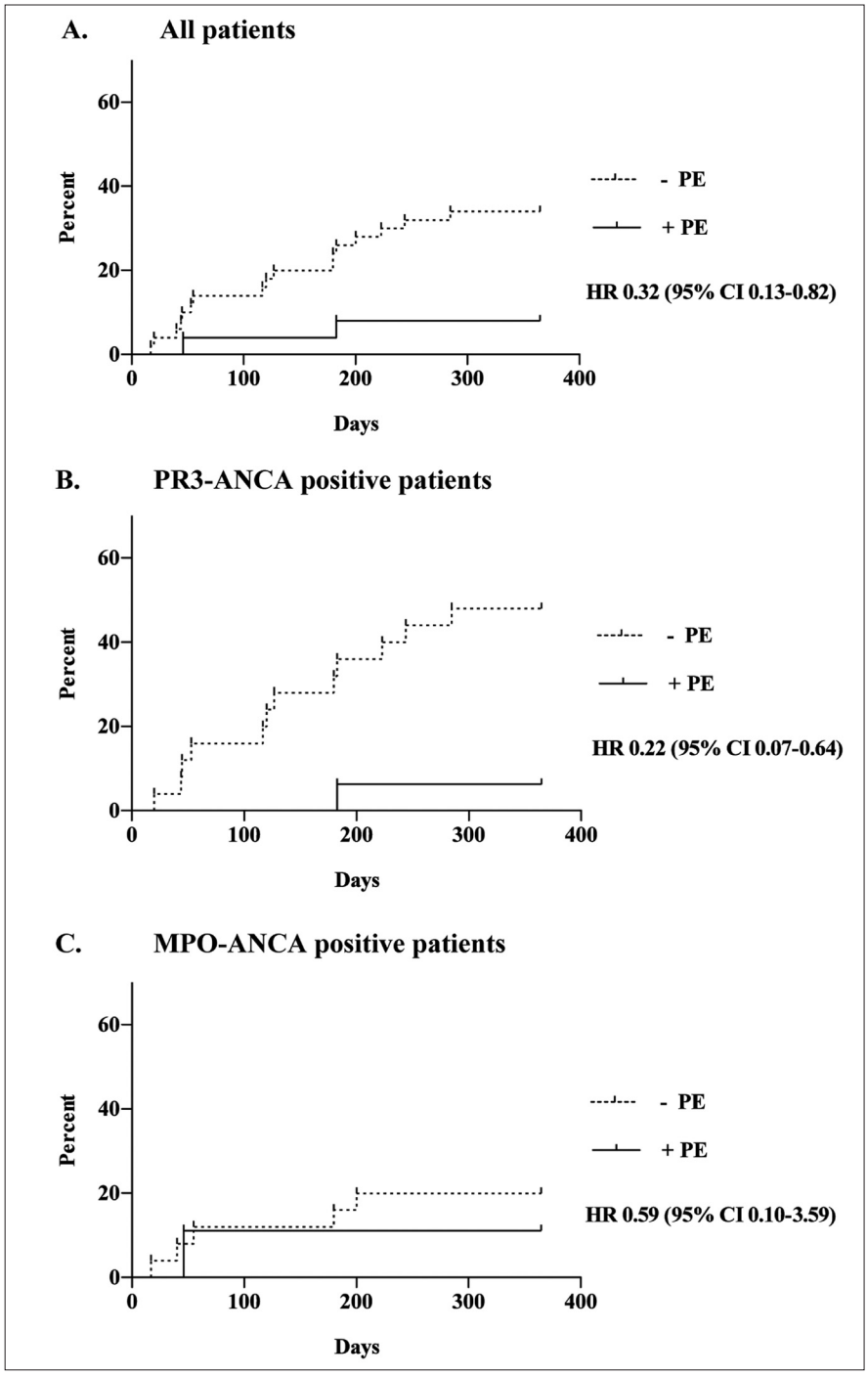

Fig. 3. The risk of relapse according to treatment group in all patients (**A**) and by ANCA subtype (**B** and **C**).

any adverse events relating directly to the PE.

Interestingly, we observed a reduced number of serious adverse events in patients receiving PE. There were no differences in the cumulated doses of steroids and CYC between the groups and we observed no correlation between the total dose of immunosuppressants and serious adverse events (data not shown). More patients in the non-PE group received MMF and fewer received AZA as maintenance therapy than patients in the PE group, but the IMPROVE study (27) comparing the efficacy and safety of AZA and MMF as maintenance agents, showed no differences in serious adverse events between the two agents. Thus, it seems likely that some of the severe events may be related to disease burden, and that faster and better control of the disease process by supplementary PE may lead to less severe disease and fewer serious adverse events. Lung involvement with haemoptysis is a severe extra-renal manifestation of vasculitis, and in this context it is interesting, that only 2/7 (29%) of the patients with haemoptysis in the PE treated group did poorly by one year (one died, one ESRD) compared to 5/6 (83%) in the non-PE group (three died, one ESRD and one experienced >3 severe adverse events). However, since PE was offered, however not systematically, to patients with haemoptysis before 2007, the result of this comparison may be significantly influenced by selection bias.

The IMPROVE study (27) published in 2007 showed that AZA is more effective than MMF in maintaining disease remission and consequently a greater fraction of patients in the PE group in our study received AZA as maintenance therapy compared to the patients in the non-PE group. This may contribute to the increased frequency of relapses in the latter, although no difference in the number of patients that received MMF or AZA was observed among the patients relapsing in our study. In a retrospective, 5-year follow-up study with 248 AAV patients, the mean time for relapse was 13 months (3) and Spritz *et al*. found that >50% of relapses developed more than 1.5 years after beginning of treatment (9). Thus, it will be of great interest to continue the follow-up of our cohort to study the potential long-term effects of early PE.

The present study is retrospective with a predominantly historical control group, which of course may introduce selection bias. Furthermore, there may have been some changes in the treatment practice during the period from 1999 to 2011, including the greater use of AZA for maintenance therapy after 2007. Finally, the conclusions and extrapolation of data are limited by the small number of patients included in this single-centre study, especially in relation to the subgroup analyses.

Despite progress in the treatment, renal AAV is still associated with a se-

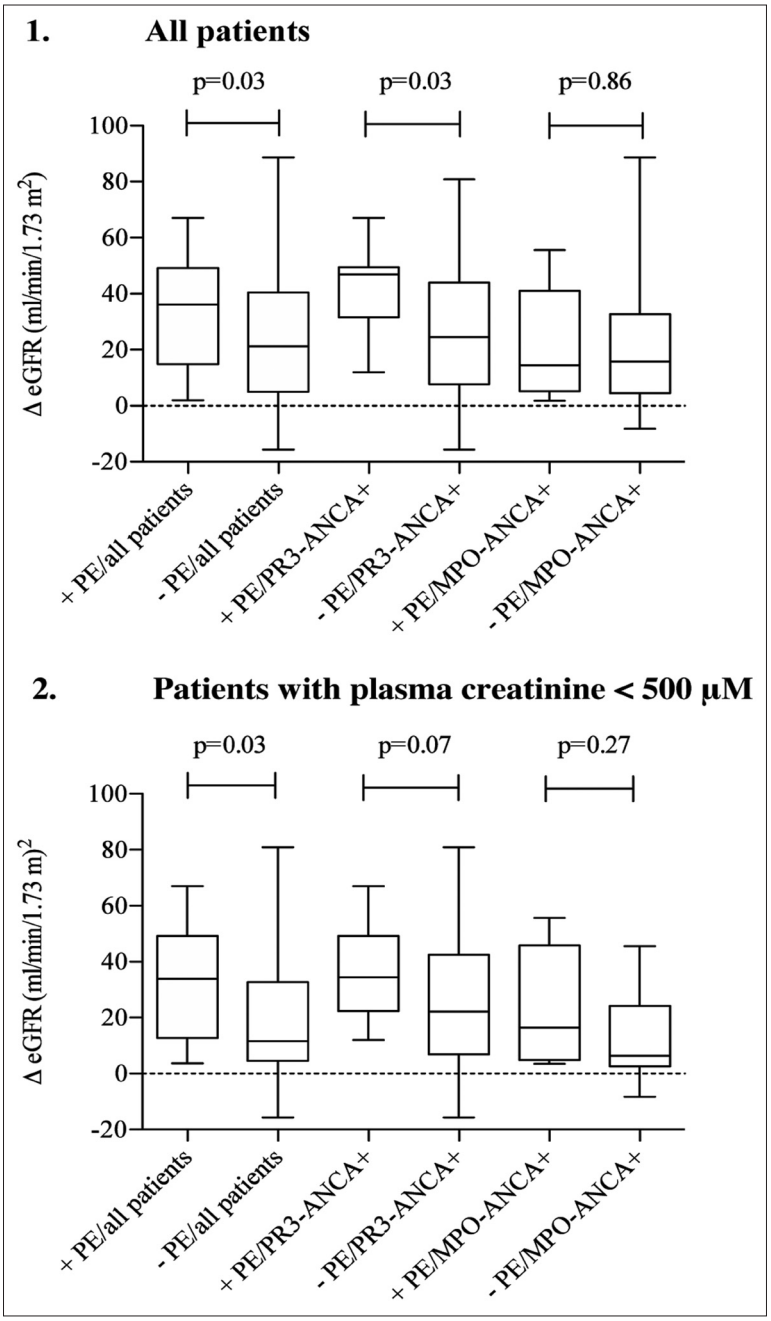

Fig. 4. The changes in eGFR among patients not on dialysis from the time of initiating immunosuppressive treatment to one-year according to treatment group in all patients and by ANCA subtype (**A**), as well as in patients with plasma-creatinine <500 µM (**B**).
Boxes represent 25%–75% percentiles with median value outlined and whiskers representing min-max values.

rious outcome and the treatment of severe AAV is not without harm (5, 28). Therefore, there is a need for new treatment modalities and regimes. In 2010 the PEXIVAS study was initiated. In this study the efficacy of PE in addition to CYC or rituximab and glucocorticoids will be examined in the treatment of renal AAV and GFR <50 ml/min (26). The results of this study will probably first be available in 2017 or 2018 and until then, we will need to base treatment choice with respect to PE at least in part on non-randomised observations. In this context, this study suggests the use of PE on top of standard induction treatment with CYC and glucocorticoids to patients with renal PR3-AVV and an eGFR <60 ml/min/1.73m^2.

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