

Clinical implication of plasma exchange on life-threatening antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Background We assessed the rate of and the predictor for all-cause mortality in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients receiving plasma exchange (PLEX) and evaluated the survival-benefit of PLEX for diffuse alveolar haemorrhage (DAH) between AAV patients receiving PLEX and those not receiving.

Methods We retrospectively reviewed the medical records of 212 AAV patients. Demographic, clinical and laboratory data at the time of PLEX was collected from both 9 patients receiving PLEX and 10 AAV patients with DAH. The follow-up duration was defined as the period from the time of PLEX or DAH occurrence to death for the deceased patients and as that to the last visit for the survived patients.

Results The median age of 9 AAV patients receiving PLEX was 71.0 years and 5 patients were men. Four of 9 patients receiving PLEX died at a median follow-up duration of 92.0 days. Three died of sepsis and one died of no response to PLEX. When patients with DAH receiving PLEX and those not receiving were compared, there were no significant differences in variables between the two groups. The cumulative patients' survival rate between patients with DAH receiving PLEX and those not receiving were also compared using the Kaplan-Meier survival analysis but no survival-benefit of PLEX for DAH was observed.

Conclusion The rate of all-cause mortality in 9 AAV patients receiving PLEX was assessed as 44.4% and it was controversial that PLEX is beneficial for the improvement of prognosis of AAV-related DAH.

Background

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is one of the small vessel vasculitides and consists of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1, 2]. The latest recommendations for the management of AAV were proposed by the European League Against Rheumatism (EULAR) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) in 2016 (the 2016 EULAR/ERA-EDTA recommendations) [3]. According to these recommendations, a combination of glucocorticoid with either cyclophosphamide (CYC) or rituximab (RTX) should be administered to newly diagnosed patients with life-threatening AAV. Once remission is achieved, azathioprine or methotrexate or RTX could be maintained and glucocorticoid may be tapered. Particularly in cases of renal failure with rapidly progressive glomerulonephritis (RPGN) or diffuse alveolar haemorrhage (DAH), plasma exchange (PLEX) should be considered [3]. In addition to the 2016 EULAR/ERA-EDTA recommendations, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for glomerulonephritis recommends PLEX for patients with rapid and severe renal vasculitis and suspicious anti-glomerular basement membrane (anti-GBM) glomerulonephritis [4]. Therefore, PLEX is not usually prescribed but is strongly recommended to patients with life-threatening AAV.

In terms of RPGN, the Methylprednisolone versus Plasma Exchange (MEPEX) clinical trial compared the efficacy between PLEX and methylprednisolone pulse therapy in 137 AAV patients with serum creatinine >5.8 mg/dL and reported that PLEX for induction exhibited a higher frequency of renal recovery [5]. In addition, another clinical trial reported that PLEX had a preventive efficacy on exacerbation of renal dysfunction in AAV patients with serum creatinine < 5.7 mg/dL in GPA patients [6]. Whereas, a long-term observational clinical study, PLEX had no significant benefit in AAV patients with serum creatinine > 5.7 mg/dL or on dialysis [7]. Moreover, recently, the data from the Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis (PEXIVAS) clinical trial reported no efficacy of PLEX for reducing the risk of both end-stage renal disease or death in 704 AAV patients [8]. In terms of DAH, several case series reported the positive efficacy of PLEX on DAH yet [9, 10]. In particular, a retrospective study including 20 AAV patients with diffusion alveolar haemorrhage reported that combination therapy with PLEX and immunosuppressive drugs was beneficial for the lung outcomes [11]. Whereas, a retrospective cohort study including 53 AAV patients with several alveolar haemorrhage reported no significant difference in mortality between PLEX and non-PLEX group [12]. Therefore, the efficacy of PLEX on life-threatening AAV may still remain controversial.

Until now, there was no study investigating the efficacy of PLEX on life-threatening AAV, such as RPGN and DAH, in a considerable number of patients except for a few case-reports in Korea. Hence, in this study, we investigated two clinical implications of PLEX on life-threatening AAV. First, we assessed the rate of and the predictor for all-cause mortality in AAV patients receiving PLEX. And then, we also assessed the survival-benefit of PLEX for DAH between AAV patients receiving PLEX and those not receiving.

Methods

Patients

We electrically reviewed the medical records of 212 AAV patients from the retrospective Severance Hospital ANCA-associated Vasculitides cohort and selected 9 AAV patients who had received PLEX for life-threatening AAV-related clinical symptoms based on the following inclusion and exclusion criteria: i) patients who had been first classified as AAV at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, from October 2000 to March 2019; ii) patients who fulfilled the 2007 European Medicines Agency algorithm for AAV and polyarteritis nodosa (the 2007 EMA algorithm) and the 2012 revised International Chapel Hill Consensus Conference vasculitides definitions [1, 13]; iii) patients who had well-documented medical records with which clinical and laboratory data at diagnosis could be reviewed and Birmingham vasculitis activity score (BVAS) version 3 and five-factor score (FFS) at the time of diagnosis could be calculated [14, 15]; iv) patients who had the results of tests for perinuclear (P)-ANCA, cytoplasmic (C)-ANCA, myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. In patients who tested positive in the indirect fluorescence assay, but negative in antigen-specific assays, P-ANCA positivity by was considered as MPO-ANCA positivity and C-ANCA positivity as PR3-ANCA positivity [16].

We also selected 4 AAV patients, who had exhibited DAH but not received PLEX, and compared clinical and laboratory data with 6 AAV patients, who had exhibited DAH and received PLEX. This study was approved by the Institutional Review Board of Severance Hospital (**4-2017-0673**), who waived the need for patient written informed consent, as this was a retrospective study.

Clinical and laboratory data

Age and male gender were collected as a demographic data at PLEX. Variant type, ANCAs, BVAS, FFS and each clinical manifestation at PLEX were assessed. Reasons for PLEX were also searched.

Methylprednisolone pulse therapy and immunosuppressive drug both before and at or after PLEX were evaluated. All immunosuppressive drugs, which had been administered prior to the initiation of PLEX, were included in 'Administered immunosuppressive drugs before PLEX' regardless of either induction or maintenance therapy. The follow-up duration was defined as the period from the time of PLEX for DAH, RPGN and cardiac tamponade to death for the deceased patients and as that to the last visit for the survived patients. Whereas, as for AAV patients with DAH not receiving PLEX, the follow-up duration was defined as the period from the time of detecting DAH to death for the deceased patients and as that to the last visit for the survived patients. The rate and the causes of all-cause mortality were assessed.

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for Windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a median (interquartile range (IQR)), and categorical variables were expressed as number and the percentage. The univariable Cox hazard model analysis was conducted to appropriately obtain the hazard ratios (HRs) of each variable for all-cause mortality. Significant differences in categorical variables between the two groups were analysed using the Chi-square and Fisher's exact tests. Significant differences in continuous variables between the two groups were compared using the Mann-Whitney test. Comparison of the cumulative patients' survival rate between the two groups was analysed by the Kaplan-Meier survival analysis.

Results

Baseline characteristics

Clinical and laboratory data are described in **Table 1**. Nine of 212 AAV patients (4.3%) had received PLEX for life-threatening AAV. The median age was 71.0 years and 5 patients were men. Six patients were classified as MPA and three patients as GPA but none as EGPA. ANCAs were detected in 6 patients but anti-GBM was not found. The median BVAS and FFS at PLEX were 20.0 and 3.0. FFP was used in all patients and there were no PLEX-related complications including bleeding. Five patients received PLEX 9 times, 2 patients received it 6 times and 2 patients received it 3 times. Six patients received PLEX for DAH,

two for RPGN and one for cardiac tamponade. Methylprednisolone pulse therapy was performed at PLEX to all nine patients. The most commonly administered immunosuppressive drugs before and at or after PLEX were CYC and RTX respectively. Four of 9 patients receiving PLEX died at a median follow-up duration of 92.0 days. Three died of sepsis and one died of no response to PLEX. Three deceased patients with DAH were all admitted to the intensive care unit (ICU) and took ventilation care along with continuous renal replacement therapy in ICU.

Predictor for all-cause mortality in AAV patients receiving PLEX

We assessed the predictive value of each variable for all-cause mortality using the univariable Cox hazards model analysis. MPO-ANCA (or P-ANCA) exhibited a high HR for all-cause mortality but it was not statistically significant (HR 5.710, P = 0.143). In addition, neither DAH nor RPGA was associated with all-cause mortality. Among immunosuppressive drugs during follow-up, RTX exhibited a tendency to reduce the rate of all-cause mortality but there was no statistical significance either (HR 0.209, P = 0.177) (**Table 2**).

Comparison between patients with DAH receiving PLEX and those not receiving

In **Table 3**, we compared variables between patients with DAH receiving PLEX and those not receiving PLEX. There were no significant differences in demographic data, AAV variants, ANCA, AAV-specific indices and immunosuppressive drugs administered between the two groups. In addition, the follow-up duration and the rate of all-cause mortality did not significantly differ. On the other hand, we compared the cumulative patients' survival rate between patients with DAH receiving PLEX and those not receiving using the Kaplan-Meier survival analysis to assess the survival-benefit of PLEX for DAH. However, we found no significant difference between the two groups, which suggested no survival-benefit of PLEX for DAH in AAV patients (**Fig. 1**).

Discussion

In this study, we derived two conclusions on the efficacy of PLEX on life-threatening AAV.

Firstly, in terms of the rate of and the predictor for all-cause mortality in AAV patients receiving PLEX, the rate of all-cause mortality was assessed as 44.4%, but no significant predictor for all-cause mortality was determined. In the MEPEX trial, the rates of all-cause mortality at 3 and 12 months were 16% and 27% in the PLEX group, which was reflective of renal involvement as the serious manifestation in combination with a high risk of infection due to immunosuppressive therapy [5]. Meanwhile, the PEXIVAS trial included two groups: 352 patients in the PLEX group and 352 in the no PLEX group based on glucocorticoid therapy. The rate of all-cause mortality and end-stage renal disease (ESRD) occurrence was 28.4% in the PLEX groups and 31.0% in the no PLEX groups. The HR of PLEX on all-cause mortality compared to no

PLEX was 0.87 (95% confidence interval 0.58-1.29). Therefore, PLEX did not have any influence on the rate of all-cause mortality or ESRD occurrence in AAV patients [8]. It could be assumed that the very high mortality rate might interfere and offset the statistical significance of the predictor of all-cause mortality after performing PLEX. Also, this may have two clinical meanings: first, the therapeutic efficacy of PLEX might not be as high as was expected. Second, the severity of AAV might exceed the therapeutic potential of PLEX on AAV.

Secondly, we compared the survival-benefit of PLEX for DAH between patients with DAH receiving PLEX and those not receiving. Most previous studies on the efficacy of PLEX have been conducted in patients with kidney involvement of AAV. Two representative clinical trials, such as MEPEX and PEXIVAS, reported the conflicting efficacy of PLEX on RPGN [5, 8]. As for AAV patients with reduced kidney function due to RPGN, there are alternative treatment-modalities in addition to PLEX: transient renal replacement together with combination therapy of high dose glucocorticoid and either cyclophosphamide or rituximab may improve RPGN [3, 4]. However, as for patients with DAH, there is no alternative treatment-modality in addition to PLEX because DAH is more rapidly progressive and fatal than RPGN. For this reason, it seems to be impossible to design and conduct randomised case-controlled clinical trials in AAV patients with urgent DAH, unlike RPGN.

There was the observational case series regarding the efficacy of PLEX on DAH in 12 AAV patients who were admitted to an intensive care unit. The authors demonstrated that PLEX together with a combination of glucocorticoid and immunosuppressive drugs might have a benefit to improve both the respiratory dysfunction and AAV-related DAH in AAV patients, although one patient died. In this study, 10 AAV patients with DAH, of whom 6 patients received PLEX, were retrospectively analysed [10]. However, unlike the previous study, this study could not find any efficacy of PLEX on DAH to improve all-cause mortality. At last, in the Kaplan survival analysis, PLEX did not increase the cumulative patients' survival rate in AAV patients with DAH. In addition, when only 6 AAV patients with DAH receiving PLEX in this study were compared with 12 patients in the previous study, the rate of all-cause mortality was significantly different, 50% vs. 10% [10].

We considered the reason for this discrepancy as the follow-up period. The previous study evaluated the SpO₂/FiO₂ ratio and assessed the mechanical ventilation mode hourly for 7 days. However, they did not evaluate all-cause mortality after extubation and during follow-up [10]. Thus, it could not be easily accepted that PLEX is beneficial for the improvement of prognosis of AAV-related DAH. Whereas, the median follow-up duration of our study is significantly longer than that of the previous study (1145.5 days for 4 patients not receiving PLEX and 130.0 days for 6 patients receiving PLEX). Of 4 AAV deceased patients with DAH, three patients died of sepsis due to secondary pneumonia one patient died of the rapid progression of DAH due to ineffectiveness of PLEX (**Table 3**).

Taken together with the results of both our and the previous studies, we would suggest the therapeutic strategies depending on the time-course. Firstly, within one or two weeks from DAH development, PLEX along with a combination of glucocorticoid with CYC or RTX should be promptly

initiated under close observation in the intensive care unit. This strategy is expected to reduce the rate of all-cause mortality at a rate from 8.3% to 10.0%. Next, after two weeks from DAH development, the most common reason for death was secondary pneumonia and sepsis. Therefore, the monitoring of pneumonia occurrence, the use of preventive antibiotics and the choice of dose or type of immunosuppressive drugs should be carefully considered.

Our study has several limitations. Firstly, we provided a narrative report rather than an analytic one, as the number of patients who received PLEX was too small to conduct a subgroup analysis. In particular, for this reason, the comparison of variables between patients with DAH and without DAH treated with PLEX was not allowed. Secondly, we could not obtain all sufficient information from the medical record such as PLEX technique, ventilator modes and lung-involvement pattern due to the limitation of a retrospective study design. Thirdly, this study analysed the data which had been accumulated over 8 years. During this period, the overall prognosis of AAV patients had been improved along with the development of the accuracy of ANCA tests and the efficacy of immunosuppressive drugs. Therefore, this might impact on the results of the retrospective and observational study. Despite these limitations, however, we believe that our study, which is based on the biggest cohort in Korea, could provide valuable information on PLEX in Korean patients with AAV. Therefore, this study has a clinical significance as a pilot study.

Conclusions

Nine of 212 AAV patients (4.3%) received PLEX and the rate of all-cause mortality in 9 AAV patients receiving PLEX was assessed as 44.4%. However, no significant predictor for all-cause mortality was determined. DAH was the most common reason for PLEX performance but it was controversial that PLEX is beneficial for the improvement of prognosis of AAV-related DAH.

Abbreviations

ANCA: Antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic GPA; EULAR: European League Against Rheumatism; ERA-EDTA: European Renal Association-European Dialysis and Transplant Association; CYC: Cyclophosphamide; RTX: Rituximab; RPGN: Rapid progressive glomerulonephritis; DAH: Diffuse alveolar haemorrhage; PLEX: Plasma exchange; KDIGO: Kidney Disease: Improving Global Outcomes; GBM: Glomerular basement membrane; MEPEX: Methylprednisolone versus Plasma Exchange; PEXIVAS: Plasma Exchange and Glucocorticoids for Treatment of AAV; BVAS: Birmingham vasculitis activity score; FFS: Five factor score; P: Perinuclear; C: cytoplasmic; MPO: Myeloperoxidase; PR3: Proteinase 3; IQR: Interquartile range; HR: Hazard ratio.

Declarations

Acknowledgments

None

Authors' contributions

PGP, BWY and SWL participate in research design, the acquisition of data, the writing of the manuscript, and the performance of the research. PGP, BWY, JJS and SWL contributed to the acquisition of data, interpretations of data, PGP, BWY, YBP and SWL participate in preparation of the manuscript and final revision. All authors read and approved the final revision of the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Severance Hospital (**4-2017-0673**), who waived the need for patient written informed consent, as this was a retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Variables	Values
Demographic data at PLEX	
Age (years)	71.0 (25.0)
Male gender (N, (%))	5 (55.6)
AAV variants (N, (%))	
MPA	6 (66.7)
GPA	3 (33.3)
EGPA	0 (0)
Gap-time from diagnosis to PLEX (days)	69.0 (127.0)
ANCA and anti-GBM within 4 weeks before PLEX (N, (%))	
MPO-ANCA (or P-ANCA)	4 (44.4)
PR3-ANCA (or C-ANCA)	2 (22.2)
ANCA negativity	3 (33.3)
Anti-GBM	0 (0)
AAV related indices at PLEX	
BVAS	20.0 (14.0)
FFS	3.0 (1.5)
Clinical manifestations at PLEX (N, (%))	
General	9 (100)
Cutaneous	1 (11.1)
Mucous membrane/Eyes	0 (0)
ENT	3 (33.3)
Pulmonary	7 (77.8)

Values are expressed as median (interquartile range (IQR)) or number (percentage).

ANCA: antineutrophil cytoplasmic antibody; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; PLEX: plasma exchange; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; GBM: glomerular basement membrane; BVAS: Birmingham vasculitis activity score; FFS: five factor score; ENT: ear nose throat; DAH: diffuse alveolar haemorrhage; RPGN: rapidly progressive glomerulonephritis; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; TAC: tacrolimus.

Variables	Values
Cardiovascular	3 (33.3)
Abdominal	0 (0)
Renal	7 (77.8)
Nervous systemic	2 (22.2)
Reason for PLEX (N, (%))	
DAH	6 (66.6)
RPGN	2 (22.2)
Pericarditis with cardiac tamponade	1 (11.1)
Methylprednisolone pulse therapy at PLEX (N, (%))	9 (100)
Administered immunosuppressive drugs before PLEX (N, (%))	
CYC	4 (44.4)
RTX	3 (33.3)
AZA	1 (11.1)
MMF	1 (11.1)
TAC	1 (11.1)
None	4 (44.4)
Administered immunosuppressant drugs at or after PLEX (N, (%))	
CYC	1 (11.1)
RTX	5 (55.6)
AZA	1 (11.1)
MMF	1 (11.1)
TAC	0 (0)

Values are expressed as median (interquartile range (IQR)) or number (percentage).

ANCA: antineutrophil cytoplasmic antibody; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; PLEX: plasma exchange; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; GBM: glomerular basement membrane; BVAS: Birmingham vasculitis activity score; FFS: five factor score; ENT: ear nose throat; DAH: diffuse alveolar haemorrhage; RPGN: rapidly progressive glomerulonephritis; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; TAC: tacrolimus.

Variables	Values
None	2 (22.2)
Follow-up duration (days)	92.0 (225.5)
All-cause mortality (N, (%))	4 (44.4)
Cause of death (N, (%)) (N = 4)	
Sepsis	3 (75.5)
No response to PLEX	1 (25.5)
Values are expressed as median (interquartile range (IQR)) or number (percentage).	
ANCA: antineutrophil cytoplasmic antibody; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; PLEX: plasma exchange; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; GBM: glomerular basement membrane; BVAS: Birmingham vasculitis activity score; FFS: five factor score; ENT: ear nose throat; DAH: diffuse alveolar haemorrhage; RPGN: rapidly progressive glomerulonephritis; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; TAC: tacrolimus.	

Table 1

Characteristics of 9 patients with AAV at the time of PLEX

Variables	HR	95% CI	P value
Demographic data at PLEX			
Age	1.007	0.952, 1.064	0.820
Male gender	1.330	0.186, 9.528	0.777
AAV variants	0.016	0.000, 60.511	0.327
ANCA within 4 weeks before PLEX			
MPO-ANCA (or P-ANCA)	5.710	0.556, 58.595	0.143
PR3-ANCA (or C-ANCA)	0.027	0.000, 231.881	0.434
ANCA negativity	0.676	0.069, 6.581	0.736
AAV related indices at PLEX			
BVAS	0.940	0.800, 1.104	0.450
FFS	1.247	0.423, 3.678	0.689
Clinical manifestations at PLEX			
General	N/A		
Cutaneous	0.041	0.000, 5961414.0	0.739
Mucous membrane/Eyes	N/A		
ENT	0.024	0.000, 119.450	0.391
Pulmonary	1.008	0.103, 9.837	0.995
Cardiovascular	0.491	0.050, 4.786	0.540
Abdominal	N/A		
Renal	0.649	0.067, 6.322	0.710
Nervous systemic	0.993	0.102, 9.69.	0.995
Reason for PLEX			

PLEX: plasma exchange; ANCA: antineutrophil cytoplasmic antibody; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five factor score; ENT: ear nose throat; DAH: diffuse alveolar haemorrhage; RPGN: rapidly progressive glomerulonephritis; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; TAC: tacrolimus.

Variables			
DAH vs. RPGN	1.544	0.139, 17.193	0.724
Administered immunosuppressant drugs during follow-up			
CYC	1.893	0.194, 18.490	0.583
RTX	0.209	0.022, 2.024	0.177
AZA	7.483	0.467, 119.824	0.155
MMF	0.038	0.000, 5830.207	0.592
TAC	N/A		
None	1.541	0.158, 15.021	0.710
PLEX: plasma exchange; ANCA: antineutrophil cytoplasmic antibody; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five factor score; ENT: ear nose throat; DAH: diffuse alveolar haemorrhage; RPGN: rapidly progressive glomerulonephritis; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; TAC: tacrolimus.			

Table 2 Univariable Cox hazards model analysis of variables for all-cause mortality

Variables	Patients with DAH not receiving PLEX (N = 4)	Patients with DAH receiving PLEX (N = 6)	P value
Demographic data at DAH			
Age (years)	56.5 (21.0)	65.5 (34.0)	0.807
Male gender (N, (%))	2 (50.0)	3 (50.0)	1.000
MPA vs. GPA (N, (%))	3 (75.0)	4 (66.7)	0.778
ANCA within 4 weeks before DAH (N, (%))			
MPO-ANCA (or P-ANCA)	3 (75.0)	2 (33.3)	0.197
PR3-ANCA (or C-ANCA)	1 (25.0)	2 (33.3)	0.778
ANCA negativity	0 (0)	2 (33.3)	0.197
AAV related indices at DAH			
BVAS	16.0 (17.0)	15.0 (13.5)	1.000
FFS	2.0 (0)	2.5 (2.25)	1.000
Steroid pulse at DHA (N, (%))	4 (100)	6 (100)	N/A
Administered immunosuppressive drugs (N, (%))			
CYC	4 (100)	5 (83.3)	0.389
RTX	0 (0)	2 (33.3)	0.197
AZA	3 (75.0)	1 (16.7)	0.065
MMF	0 (0)	2 (33.3)	0.197
TAC	0 (0)	1 (16.7)	0.389
None	0 (0)	1 (16.7)	0.389

Values are expressed as median (interquartile range (IQR)) or number (percentage).

DAH: diffuse alveolar haemorrhage; PLEX: plasma exchange; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; BVAS: Birmingham vasculitis activity score; FFS: five factor score; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; TAC: tacrolimus.

Variables	Patients with DAH not receiving PLEX (N = 4)	Patients with DAH receiving PLEX (N = 6)	P value
Follow-up duration (days)	1145.5 (3421.5)	130.0 (291.8)	0.080
All-cause mortality (N, (%))	1 (25.0)	3 (50.0)	0.429
Values are expressed as median (interquartile range (IQR)) or number (percentage).			
DAH: diffuse alveolar haemorrhage; PLEX: plasma exchange; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; BVAS: Birmingham vasculitis activity score; FFS: five factor score; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; TAC: tacrolimus.			

Table 3
Comparison of variables between patients with DAH receiving PLEX and those not receiving

Figures

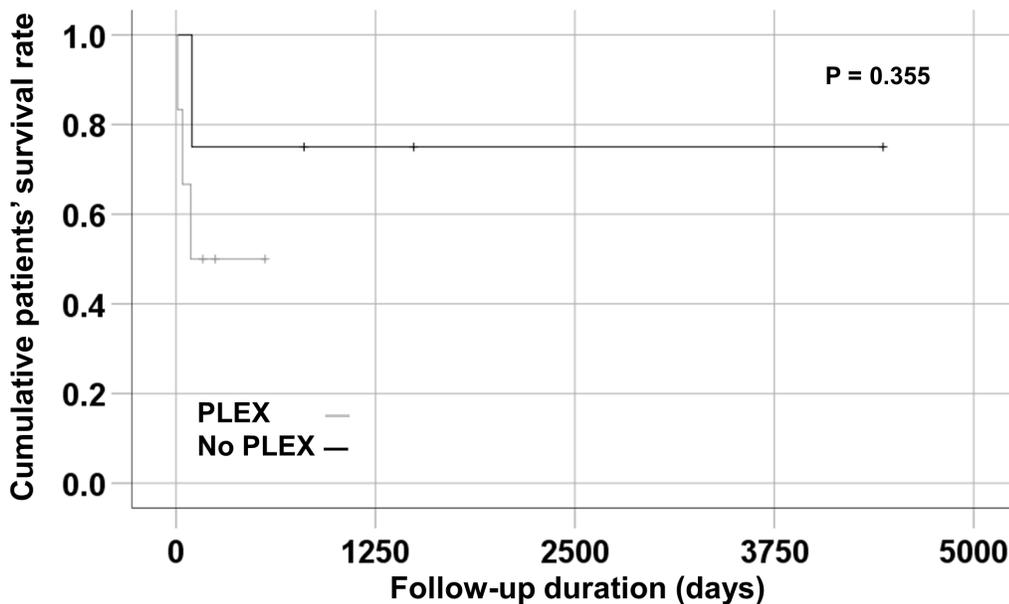


Figure 1

Comparison the cumulative patients' survival rate between patients with DAH receiving PLEX and those not receiving. No significant difference between the two groups was observed, which suggested no survival-benefit of PLEX for DAH in AAV patients. DAH: Diffuse alveolar haemorrhage; PLEX: Plasma exchange; AAV: Antineutrophil cytoplasmic antibody-associated vasculitis.