Plasma exchange for severe alveolar hemorrhage in ANCA-associated vasculitis: emulation of a target trial

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ACS, SG, RP, NDP and BT prepared study protocol. ACS and SG extracted data, and SG and RP did the statistical analysis. ACS, SG, RP, NDP and BT wrote the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. C. Desnos, R. Lombardi, J. Malherbe, D. Titeca-Beauport, F. Reizine, G. Louis, K. Nassarmadji, J. Campagne, JP. Martellosio, A. Deroux, E. Bendiab, V. Coirier, J. Catano, M. Pineton De Chambrun, M. Samson, C. Vigneron, M. Samson, A. Neel, P. Smets, T. Deltombe, B. Brilland, M. Desgrouas, O. Simon, S. Faguer, S. Giorgiutti, R. Paule, F. Arrive, I. Masson, T. Quémeneur, CA. Durel, E. de Montmollin, JP. Quenot, F. Perrin, H. Lobbes, Q. Lajoye, R. Mesbah, R. Outh, B. Thoreau, A. Lacraz, C. Philipponnet, D. Contou, F. Parazols, F. Garo, G. Blonz, G. Ducoux, H. Yildiz, I. Rey, L. Di Ascia, N. Issa, P. Le Guen, V. Queyrel, R. Eid, R. Arcani, Y. Uzunhan, X. Puéchal completed patients data and reviewed the manuscript.

Transparency declaration

The manuscript guarantor, Benjamin Terrier, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that there are no discrepancies from the study as planned.

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At a Glance Commentary

Scientific Knowledge on the Subject

Plasma exchange (PLEX) is an attractive treatment for ANCA-associated vasculitides, but studies to date have yielded mixed results, particularly in patients with diffuse alveolar hemorrhage (DAH).

The PEXIVAS study, which evaluated plasma exchange in ANCA-associated vasculitides, did not show a significant benefit on death or end-stage renal disease, although its applicability to patients with severe DAH was limited by the small proportion of such patients in the study population.

Current recommendations for the use of PLEX in severe AAV-related DAH are conflicting, highlighting the need for targeted research to clarify its impact, particularly in the intensive care setting.

What This Study Adds to the Field

This study shows that the addition of plasma exchange to standard care for DAH in the intensive care unit had no effect on 30-day mortality.

It provides further evidence for the need to re-evaluate guidelines for plasma exchange in the most severe patients with ANCA-associated vasculitides.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

This article has an online data supplement, which is accessible at the Supplements tab.

Abstract

Rationale. Patients with severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)-related diffuse alveolar hemorrhage (DAH) face high mortality. In the PEXIVAS trial, plasma exchange (PLEX) did not reduce death or end-stage kidney disease, but only 9% had severe DAH.

Objectives. This study aimed to assess whether PLEX lowers mortality in patients with severe DAH.

Methods. We emulated a target trial using retrospective data from a national multicenter cohort of patients with severe AAV-related DAH. The primary endpoint was 30-day mortality after ICU admission, analyzed using a Cox model adjusted for prespecified confounders.

Main Results. We included 184 patients (median age 66 [53–75] years; 51% female; 51% with granulomatosis with polyangiitis; 53% MPO-ANCA positive). Of these, 144 (78.3%) received PLEX and 40 (21.7%) did not. Baseline characteristics were similar, except for more severe renal impairment (creatinine 357 vs. 171 µmol/L, P=0.01) and more frequent cyclophosphamide use (77% vs. 55%, P=0.01) in the PLEX group. Severity at ICU admission (median SAPS II score: 42) and mechanical ventilation needs (54%) were comparable between groups. At 30 days, overall survival was 85%. No significant difference in mortality was observed between the PLEX and no-PLEX groups: 30-day survival was 85% (95% CI 81–90) with PLEX vs. 88% (95% CI 77–96) without (HR 1.23; 95% CI 0.57–3.89). Secondary outcomes were also similar.

Conclusion. In this emulated target trial, PLEX did not reduce 30-day mortality in patients with severe AAV-related DAH.

Key words: ANCA-associated vasculitis, alveolar hemorrhage, plasma exchanges, mortality

Word Count: 234 words

Introduction

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) with significant morbidity and mortality[1]. Among the most severe manifestations, acute respiratory failure and acute kidney injury are the leading causes of intensive care unit (ICU) admission in AAV[2]. Patients with diffuse alveolar hemorrhage (DAH) have a high early mortality, mostly related to active vasculitis and treatment toxicity[3,4]. Since ANCA are involved in the pathophysiology of the disease[5], plasma exchange (PLEX) is an attractive treatment for severe AAV. The efficacy of PLEX in AAV may be related to the rapid clearance of ANCA, but also to the removal of inflammatory mediators and coagulation factors[6]. Its efficacy has been studied in various clinical settings with mixed results leading to conflicting recommendations.

In the MEPEX study[7], patients with a serum creatinine level >500 μmol/L who received PLEX had a better 3-month and 12-month renal survival than those who received methylprednisolone pulses, both in addition to glucocorticoid (GC) and cyclophosphamide. However, 12-month survival, long-term survival and long-term renal survival were not significantly improved by PLEX[8]. Later, the PEXIVAS trial[9] evaluated the use of PLEX in patients with severe AAV, defined by an estimated glomerular filtration rate <50 mL/min/1.73 m^2 and/or DAH. In this trial, PLEX showed no significant effect on the incidence of death and end-stage kidney disease (ESKD). However, only 27% of patients had any degree of DAH, and less than 9% had severe DAH, defined by an oxygen saturation of 85% or less while the patient was breathing ambient air or the need mechanical ventilation.

Among patients with severe DAH, the number of deaths was higher in the no-PLEX group, but the number of events observed was small and statistical analyses did not show a significant difference[10].

The 2022 EULAR recommendations on AAV[11] did not recommend the routine use of PLEX in DAH whereas the 2024 KDIGO recommendations[12] proposed considering PLEX for patients with DAH and hypoxemia. Overall, these discrepancies in recommendations suggest that the role of PLEX in patients with severe AAV- related DAH needs to be clarified.

In the present study, we aimed to evaluate whether PLEX reduces early mortality in patients with severe AAV- related DAH admitted to the ICU by emulating a target trial. Some of the results of this study have been previously reported in the form of an abstract(s)[13] [14].

Methods

Design of the study

We emulated a target trial based on the analysis of a national multicenter observational and retrospective database of patients with severe AAV- related DAH. Data were retrospectively extracted from medical records and entered into a CRF by ICU and non-ICU physicians from the internal medicine, nephrology, pulmonology, or rheumatology departments of 42 centers participating in either the French Vasculitis Study Group (FVSG) network or the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (GRRR-OH).

Patients

We included patients who were 1) older than 15 years, 2) with a severe episode of DAH associated with newly diagnosed or relapsing AAV (GPA or MPA) between November 2012 and January 2024. DAH was defined as respiratory symptoms (cough, dyspnea, sputum production) associated with new pulmonary infiltrates consistent with this diagnosis, and

either hemoptysis or endoscopic findings suggestive of DAH (hemorrhagic bronchoalveolar lavage or Golde score >100 [15]) or unexplained anemia. Severe DAH was defined by an oxygen saturation of 85% or less while the patient was breathing ambient air, or the need for oxygen (≥6 L/min) or mechanical ventilation.

Exclusion criteria included alternative diagnoses for DAH such as pulmonary edema, other conditions requiring PLEX (acute thrombotic microangiopathy, acute myasthenia gravis, anti-GBM vasculitis, hyperviscosity syndrome), or a decision to not initiate PLEX or organ support (invasive and non-invasive ventilation, extracorporeal support, catecholamines, and renal replacement therapy) on admission to the ICU because of patient's frailty or refusal of treatment.

Medical characteristics were collected by ICU and non-ICU physicians, either directly responsible for patient care or affiliated with the centers where the patients had been previously managed, and included: age, gender, medical history, presentation of vasculitis at diagnosis and relapse, and presentation of DAH. We collected data on treatments including PLEX, number of procedures and modalities, glucocorticoid (GC) regimens, use of immunosuppressive agents, and anticoagulation strategies. Organ support (oxygen therapy, invasive and non-invasive ventilation, duration of ventilation, extracorporeal support, catecholamines, and renal replacement therapy) was also reported. Simplified acute physiology score (SAPS II)[16] and Birmingham vasculitis score version 3 (BVAS 2003)[17] were assessed.

Patient and Public Involvement

It was not possible to involve patients in the design, or conduct, or reporting, or dissemination plans of our research as we collected retrospective data from critically ill patients.

Endpoints

The primary endpoint was 30-day mortality after ICU admission between the PLEX and no-PLEX treatment groups.

Secondary endpoints were 90-day and 180-day mortality, duration of mechanical ventilation, length of ICU and hospital stay, and adverse effects of PLEX.

Statistical analysis

In previous studies, ICU and 28-day mortality of patients with severe AAV was 16%[2,18]. In the PEXIVAS study[9], the 3-month mortality of patients with DAH was 16% in the PLEX group versus 30% in the no-PLEX group. To detect a 14% difference in mortality (16% severe DAH with PLEX versus 30% severe DAH without PLEX) with 80% power and a 5% alpha risk, 109 patients per group would need to be enrolled in the target trial.

Demographic data are presented as numbers and percentages for categorical data and median and interquartile range (IQR) for quantitative data, unless otherwise noted, and compared using the chi-squared or Fisher test for categorical data and the two-sample t-test or Wilcoxon rank-sum test for quantitative data, respectively.

For emulating the clinical trial (**Table E1**), we set the intervention treatment as PLEX therapy, defined as any PLEX performed, regardless of modality, initiated during the episode in addition to standard induction therapy. The control group was defined as patients admitted to the ICU with severe DAH who did not receive PLEX. The maximum time interval between severe DAH (ICU admission) and PLEX was 7 days (grace period). The grace period during emulation is the time during which patients must have received the intervention following their inclusion in the study. It represents the timeframe allowed to initiate treatment after randomization in the target trial[19]. Patients who received PLEX prior to ICU admission were not included in the emulated cohort. For patients who underwent PLEX on the day of ICU admission, the delay between ICU admission and PLEX was considered to be 0.5. To avoid

immortality bias and minimize bias by confounding, we used the clone–censor–weight design: two identical copies (clones) of patients were created in each treatment groups, as if they were equally likely to receive PLEX or not at enrollment. This ensures that patient characteristics are balanced upon ICU admission (time 0). The follow-up times of the clones were censored in each arm if they deviated from the planned protocol: patients who received PLEX within 7 days were censored at the time of the first PLEX in the control arm, and patients who did not receive PLEX within 7 days were censored at day 7 in the intervention arm (artificial censoring)[19]. To deal with the informative artificial censoring of clones, we performed an inverse probability censoring weighting using a Cox regression model with preselected confounding variables based on literature and clinical knowledge (age and ANCA type, BVAS, serum creatinine level >300 µmol/L during the episode, hemoptysis at diagnosis of DAH; SAPS II, invasive mechanical ventilation during the first 7 days after ICU admission, intra-venous cyclophosphamide and methylprednisolone pulses). Missing continuous data required for censoring weights were imputed using linear regression. Weights were truncated at the 99th percentile to avoid undue influence of outliers. Follow-up was censored at 30 days for the primary outcome. Mortality was compared by treatment group using Cox proportional hazards models. The final model was presented with hazard ratios and their 95% confidence intervals (95% CI), 30-day survival (%) with survival difference and 95% CI, and 30-day adjusted mean survival with its 95% CI. The 95% confidence intervals for the 30-day survival difference and the restricted mean survival time (RMST) difference were obtained by bootstrapping with 1000 replicates.

All tests were two-sided. STROBE[20] and CONSORT[21] guidelines were followed. Data were pooled and analysed using R 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria)[22].

Ethics

This study was conducted in accordance with the Good Clinical Practice protocol and the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the French Intensive Care Society, Paris (number: CE SRL 23-077). There was no source of funding for this study. There was no patient/public contributor in this study.

Results

Characteristics of patients in the original cohort

One hundred and ninety-seven patients met the inclusion criteria (**Figure 1**). Of these, 184 patients (median age 66 years [53, 75], female 51%) from 42 centers in France and Belgium were included in the emulation cohort (**Figure 1, Figure E1**). One hundred and forty-four (78.3%) patients received PLEX whatever the delay, and 40 (21.7%) patients did not (no-PLEX group) (**Figure E1**). Characteristics and evolution of these patients are presented, table E2, E3, and E4. In the PLEX group, patients received a median of 7 PLEX [5, 7] in 8 days [6, 14] (**Table 3**). Albumin was used as the replacement fluid in 27% of cases, frozen plasma in 28%, and a mixture of the two in 35% (table E4).

Emulated trial: baseline patient characteristics

By the end of the grace period, 130 patients were assigned to the PLEX strategy group (received PLEX within the first 7 days after ICU admission), and 53 patients were allocated to the control group (Table 1). Age and gender ratio were similar between patients who received PLEX and those who did not (**Table 1**). Ninety-four out of 184 (51%) patients had granulomatosis with polyangiitis and 90/184 (49%) had microscopic polyangiitis, while 87/184

(47%) of them had PR3-ANCA and 98/184 (53%) had MPO-ANCA. Vasculitis was newly diagnosed in 156/184 (85%) patients and 28/184 (15%) had a relapsing disease.

Severity of the disease at ICU admission

Patients had concomitant renal involvement in 161/184 (88%) of cases (**Table 2**). At ICU admission, organ involvement was similar between groups except for more severe renal impairment with a higher serum creatinine level (354 [IQR: 202,512]vs. 217 µmol/L [IQR: 96,521]) in the PLEX group. The median BVAS score was 21 [18, 26] and was similar in both groups.

At diagnosis of DAH, 90% of patients had lung infiltrates on CT scan and 73% underwent bronchoalveolar lavage (BAL) (**Table 2**). Patients receiving PLEX presented more often with hemoptysis (76% vs 57%). There was no significant difference in disease severity between groups according to SAPS II score, with a median SAPS II score of 42 (IQR 31-55) (**Table 2**).

Patient management

Treatment of AAV differed between the two groups (**Table 3**). One hundred twenty-four of 144 patients (98%) in the PLEX group received pulses of methylprednisolone compared to 48/53 (91%) in the no-PLEX group. Patients in the PLEX group were also more likely to receive intravenous cyclophosphamide (78% vs. 60%). The GC regimen after pulses of methylprednisolone did not differ between groups (**Figure E2**). Induction treatments did not differ over time (Figure E3).

All patients were admitted to the ICU. Organ support did not differ significantly between groups, with 85/184 (46%) patients requiring high-flow oxygen therapy with a median peak FiO2 of 66% [42, 80] and 99/184 (54%) patients requiring invasive mechanical ventilation

(IMV), 76/99 (77%) of whom within the first 24 hours after ICU admission. Other ICU interventions, including use of neuromuscular blocking agents, prone positioning, extracorporeal life support, vasopressor support, and need for renal replacement therapy, did not differ significantly between groups.

Primary outcome

At 30 days, 156/184 (85%) patients were alive. After group balancing by cloning and censoring in the emulated cohort (**Figure E4**), there was no difference in 30-day survival according to PLEX treatment (**Table 4**, and **Figure 2**): 30-day survival was 85% (95%CI 80-90) in the PLEX group, versus 88% (95%CI 78-96) in the no PLEX group (HR 1.27, 95%CI 0.61-3.95).

Secondary endpoints

One hundred and twenty-eight out of 184 patients (76%) were alive at 90 days and 121/184 patients (73%) were alive at 180 days with no difference in 90-day and 180-day mortality between groups (HR for 90-day mortality 1.10, 95%CI 0.59-2.37; HR for 180-day mortality 1.29, 95%CI 0.69-2.78). Median IMV duration was not significantly different between groups. Median ICU and hospital lengths of stay were 13 days [7,20] and 44 days [34,56], respectively, and were similar in both groups. (**Table 5**).

Side effects were reported in 70/144 (49%) patients receiving PLEX, including 34 serious infections, 13 serious bleeding, and 4 deaths related to side effects (3 hemorrhagic shocks and 1 hemorrhagic stroke, table E5).

Discussion

In this large cohort of patients with severe AAV- related DAH, this target trial emulation study shows that the addition of PLEX did not affect 30-day mortality.

Along with acute kidney injury, DAH is one of the most severe and life-threatening manifestations of AAV. The present study is, to our knowledge, one of the largest cohorts of patients with severe DAH, all of whom were admitted to the ICU and more than half of whom required invasive mechanical ventilation. This study provides some insight into the management of AAV- related DAH over the past decade, as patients were enrolled between 2012 and 2024, i.e. before and after the PEXIVAS trial.

The main treatment options for severe patients include the combination of GC and immunosuppressive agents, mainly cyclophosphamide, and in some cases the addition of PLEX. Approximately three quarters of the patients received PLEX. The frequent use of PLEX in our cohort has several explanations. First, acute kidney injury was common in our cohort (88%), with 61% of patients having a serum creatinine level greater than 300 μmol/L. Following the PEXIVAS trial, PLEX is still recommended for rapidly progressive glomerulonephritis according to the recent KDIGO and EULAR guidelines[11,12]. Second, two-thirds of our patients were treated after the results of the MEPEX trial and before the results of the PEXIVAS trial[9], which ultimately showed no effect of PLEX on the incidence of death and/or ESKD. However, 57 patients received PLEX after February 2020, the publication date of the PEXIVAS study, including 26 patients without severe renal impairment. This reflects the belief of vasculitis specialists and intensivists in France regarding the potential efficacy of PLEX in severe AAV- related DAH, mainly due to the lack of data in these patients. Our target trial emulation study confirms the results of PEXIVAS and its secondary analysis[10] but with a larger number of patients with severe DAH and provides additional evidence not to support the use of PLEX in these patients.

In the present study, baseline characteristics and severity scores were similar between patients who received PLEX and those who did not, except for more severe renal involvement and a higher likelihood of cyclophosphamide induction regimen in patients who received PLEX. This is due to recommendations[11,12] supporting cyclophosphamide and PLEX for the most severe renal involvement. However, the weighting allowed for balanced groups, especially for these characteristics.

As the PEXIVAS study questioned the efficacy of PLEX in rapidly progressive glomerulonephritis, Nezam *et al.* sought to determine which subset of patients with aggressive kidney disease might benefit from PLEX[23]. Similarly, our study focused on the most severe subset of patients with respiratory failure and sought to determine whether they might benefit from PLEX. However, despite the very severe form of our patients, with high oxygen requirements and frequent need for organ support, including mainly invasive mechanical ventilation, no beneficial effect could be demonstrated. To explain the lack of efficacy of PLEX in patients with severe DAH, one hypothesis could be the lack of efficacy in AAV, as supported by the PEXIVAS trial[9]. Another hypothesis could be that a potential beneficial effect of PLEX in severe DAH may be outweighed by a detrimental effect of the procedure itself, in particular the known increased risk of bleeding and infection. Indeed, in a critically ill population with DAH, techniques that use coagulation factors could have significant morbidity that would outweigh any potential benefit. Only 9% major bleeding was reported in the PLEX group, which is consistent with previous studies[24], but a role for PLEX in exacerbating alveolar hemorrhage cannot be ruled out.

This study has several limitations as well as strengths. First, it is not a randomized controlled trial and therefore may be subject to the biases inherent to its retrospective design. However, the use of emulation through the cloning-censoring weighting technique[19,25] allowed

comparability between groups for the primary outcome measure. The results therefore appeared robust and were similar to previous studies[9,10]. Conducting a randomized controlled trial, especially in the most severe population of DAH, seems impossible due to the rarity of these forms. This study has limited statistical power, and this should be taken into account when interpreting the results. Indeed, at the end of the grace period, there were 126 participants in the PLEX group and 53 in the no-PLEX group. Given the weights, the effective sample sizes were 120.6 and 44.1, respectively, corresponding to a 60.5% power to detect a 14% absolute decrease in mortality in our study. However, the PEXIVAS trial involved only 61 patients with severe DAH (31 in the PLEX group, and 30 in the no-PLEX group). As a nationwide study involving 42 centers over 11 years, it provides more robust data on this rare condition, and it would probably not be possible to recruit larger sample sizes. Moreover, a seven-day grace period may be excessively long in patients with severe DAH and could potentially obscure a benefit of very early PLEX administration (<48 hours). Also, complications of PLEX were assessed and described only by the physicians taking care of the patients. The role of PLEX in the occurrence of the adverse events could not be externally confirmed and could not be compared with the control group where anticoagulation and adverse events related to other treatments were not reported. Finally, given the retrospective nature of the study and the fact that anticoagulant strategies (systemic heparin or regional citrate) were not specifically evaluated, it is difficult to conclude whether the lack of a beneficial effect of PLEX is due to complications related to PLEX in this critical population or to a true lack of effect of PLEX, although the latter hypothesis is probably the most likely to date.

Overall, in this large population of patients admitted to the ICU for severe AAV-related DAH, this target trial emulation study shows that the addition of PLEX did not affect 30-day

mortality, which was 15% in both groups. This study suggests that the effect of PLEX, even in the most severe AAV-related DAH is limited.

Data sharing statement

Anonymized data could be made available upon reasonable request to the corresponding author.

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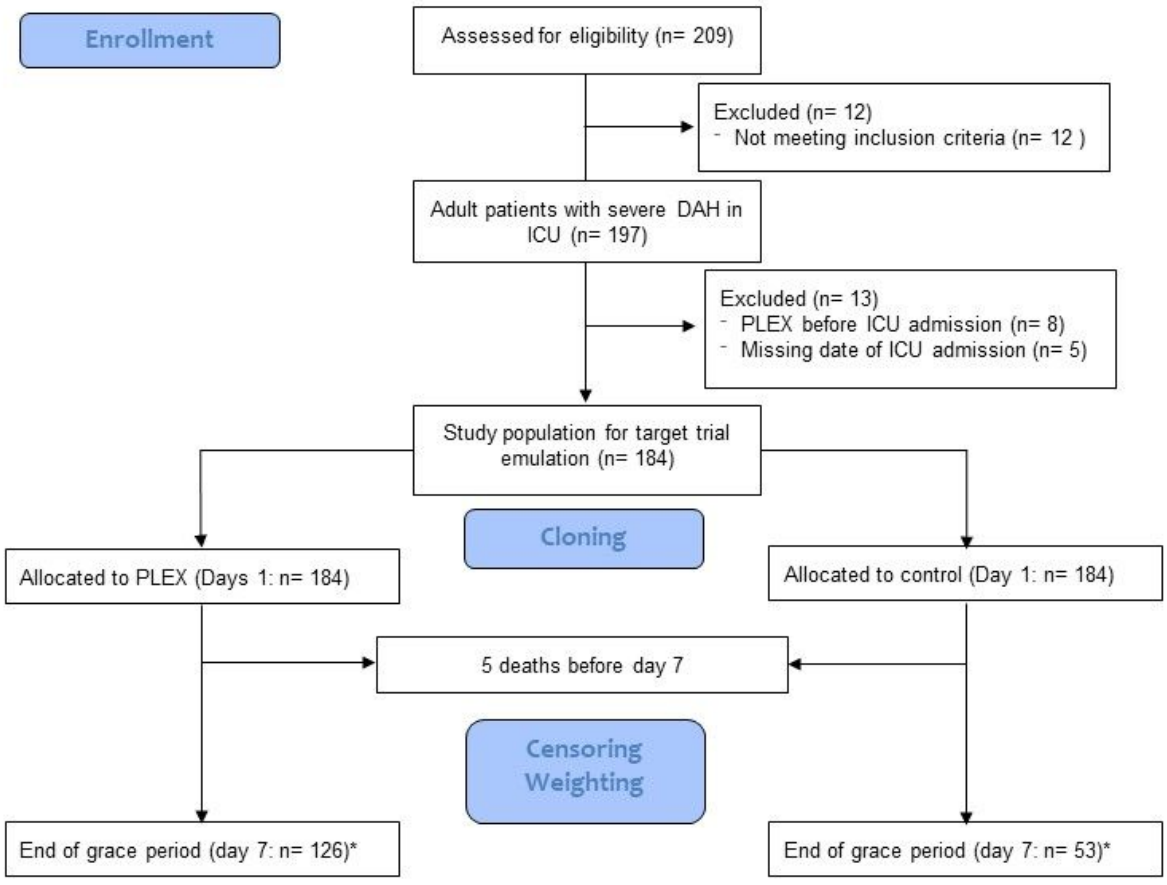
Tables and figures

Figure 1. Study flow chart.



PLEX: plasma exchange; ICU: intensive care unit.

* Includes only patients who remained compatible with each arm by day 7 (not artificially censored).

Figure 2. Weight-adjusted 30 days survival probabilities for patients with severe diffuse alveolar hemorrhage (n=184), according to treatment arm.

Blue line shows the control group and red line shows the plasma exchange (PLEX) group. Due to the cloning component of the analysis, the number at risk at day 0 is the total number of eligible patients in both arms

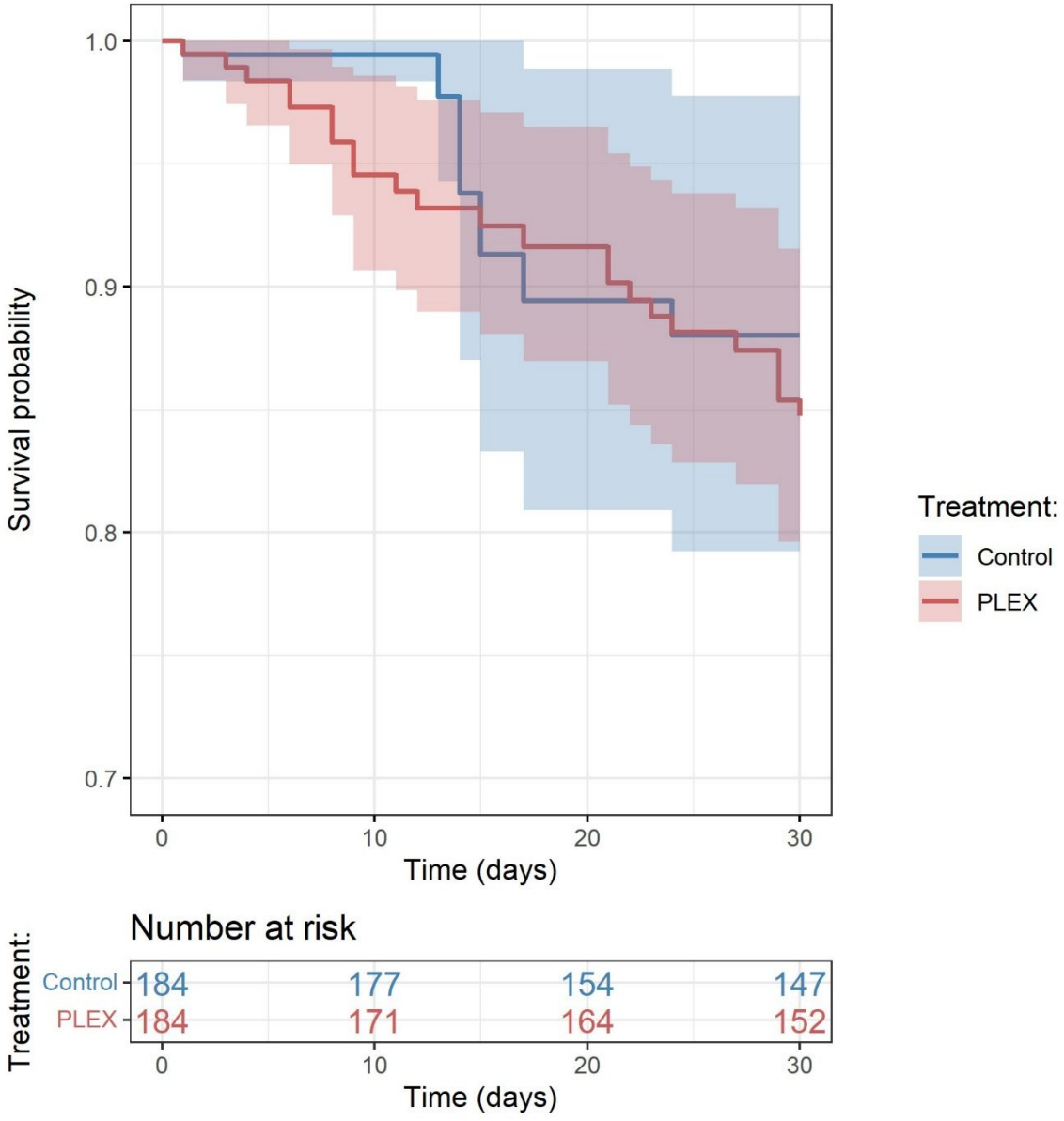


Table 1. Baseline characteristics of the 184 patients enrolled in the emulated trial, according to plasma exchange (PLEX) group, after cloning and censoring.

	Missing values	Whole sample (N=184)	Unweighted*			Weighted		
			No PLEX (N=53)	PLEX (N=126)	SMD	No PLEX (N=177)	PLEX (N=176)	SMD
Demography								
Age	0	66 [53,75]	66 [57,76]	65 [51,72]	0.184	66 [53, 76]	65 [52, 73]	0.062
Female gender	0	93 (50.5)	29 (54.7)	60 (47.6)	0.142	91 (51.2)	85 (48.4)	0.056
Vasculitis diagnosis								
GPA	0	94 (51.1)	24 (45.3)	69 (54.8)	0.19	84 (47.5)	94 (53.6)	0.121
MPA	0	90 (48.9)	29 (54.7)	57 (45.2)	0.19	92 (52.5)	82 (46.4)	0.121
ANCA type								
PR3-ANCA	0	87 (47.3)	23 (43.4)	63 (50.0)	0.133	82.2 (46.2)	84.5 (47.9)	0.034
MPO-ANCA	0	98 (53.3)	30 (56.6)	64 (50.8)	0.117	95 (53.5)	93 (52.6)	0.018
Episode Newly diagnosed	0	156 (84.8)	46 (86.8)	105 (83.3)	0.097	149 (84.6)	143 (81.2)	0.089
Relapsing	0	28 (15.2)	7 (13.2)	21 (16.7)	0.097	27 (15.4)	33 (18.8)	0.089

Results are N (%), or medians (interquartile range); ANCA: Anti Neutrophil Cytoplasmic Antigen; PR3: Proteinase 3; GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis; Two-tailed p-values come from unadjusted comparisons using Chi square or Fisher's exact tests for categorical variables, and t-tests or Mann-Whitney tests for continuous variables, as appropriate. No adjustment for multiple comparisons was performed.

* Includes only patients who remained compatible with each arm by day 7 (not artificially censored)

Table 2. Disease characteristics of the 184 patients enrolled in the emulated trial, according to plasma exchange (PLEX) group, after cloning and censoring.

	Missing values	Whole sample (N=184)	Unweighted*			Weighted		
			No PLEX (N=53)	PLEX (N=126)	SMD	No PLEX (N=177)	PLEX (N=176)	SMD
DAH characteristics								
Pulmonary infiltrates	0	165 (89.7)	45 (84.9)	115 (91.3)	0.197	147.4 (83.3)	158.9 (90.3)	0.208
BAL	0				0.043			0.045
Hemorrhagic		131 (71.2)	39 (73.6)	91 (72.2)		127.7 (72.2)	127.8 (72.7)	
Golde score >200		3 (1.6)	1 (1.9)	2 (1.6)		2.4 (1.4)	3.3 (1.9)	
Golde score	138	134 [100,184]	151 [102,183]	131 [85,182.5]	0.086	141.9 [100,179.5]	133 [74.6,180]	0.079
Hemoptysis	0	128 (69.6)	30 (56.6)	96 (76.2)	0.424	119.4 (67.1)	124.3 (70.5)	0.074
Hemoglobin level#	17	7.5 [6.6,8.6]	8 [7,9]	8 [7,8]	0.326	8 [7,9]	8 [7,8]	0.375
Minimal SpO2* (%)	59	84 [79,86]	82 [80,85]	85 [78,87]	0.032	82 [80,85]	84 [77,87]	0.13
Nasal cannula/face mask	0	11 (6.0)	3 (5.7)	8 (6.3)	0.029	11.9 (6.7)	11.6 (6.6)	0.004
Nonrebreather mask	3	103 (56.9)	28 (54.9)	71 (56.8)	0.038	91.7 (54.2)	99 (56.7)	0.049
CT findings								
Pulmonary nodule	0	30 (16.3)	8 (15.1)	20 (15.9)	0.022	27.4 (15.5)	28.5 (16.2)	0.019
Excavated nodule	0	10 (5.4)	6 (11.3)	4 (3.2)	0.318	18.3 (10.3)	5.2 (3)	0.299
Condensations	0	104 (56.5)	31 (58.5)	69 (54.8)	0.075	105.6 (59.7)	96.7 (55)	0.097
Other manifestations	0	117 (63.6)	37 (69.8)	76 (60.3)	0.2	128.2 (72.5)	106.4 (60.5)	0.258
Renal involvement	0	161 (87.5)	43 (81.1)	114 (90.5)	0.27	139.6 (79.0)	158.7 (90.2)	0.316
Creatinine level (µmol/L)#	15	335 [162,512]	217 [96,521]	354 [202,512]	0.221	278 [121,562]	331 [182,506]	0.021
Creatinine level >300 µmol/L	6	101 (56.7)	25 (47.2)	78 (61.9)	0.299	99.5 (55.9)	102.4 (58.1)	0.044
eGFR, mL/min/1.73m2	60	16 [7,40]	27 [123,58]	15 [7,36]	0.378	20 [8,54]	15 [7,38]	0.309
Proteinuria (g/L)	42	138 (84.1)	41 (85.4)	95 (85.6)	0.005	132.3 (86.9)	132.4 (85.5)	0.04
Hematuria	10	117 (67.2)	32 (64)	84 (70.6)	0.141	100.1 (62.8)	118.2 (710)	0.175

Constitutional signs	1	154 (84.2)	46 (86.8)	104 (83.2)	0.101	144.6 (81.8)	145.5 (83.3)	0.04
Fever	1	84 (45.9)	22 (41.5)	61 (48.8)	0.147	59.6 (33.7)	82.4 (47.2)	0.276
Asthenia	1	134 (73.2)	39 (73.6)	91 (72.8)	0.018	124.9 (70.6)	128 (73.3)	0.059
Weight loss	1	58 (31.7)	14 (26.4)	41 (32.8)	0.14	40.8 (23.1)	56.4 (32.3)	0.207
Joint pain	2	48 (26.4)	12 (22.6)	35 (28.2)	0.128	32.0 (18.1)	46.5 (26.8)	0.21
Arthritis	1	9 (4.9)	1 (1.9)	8 (6.4)	0.228	2.3 (1.3)	11.3 (6.5)	0.271
Myalgia	1	26 (14.2)	8 (15.1)	17 (13.6)	0.043	24.0 (13.6)	24.1 (13.8)	0.007
Cutaneous involvement	0	27 (14.7)	7 (13.2)	20 (15.9)	0.076	23.7 (13.4)	28.0 (15.9)	0.071
Purpura	0	21 (11.4)	5 (9.4)	15 (11.9)	0.08	14.8 (8.4)	21.2 (12)	0.121
ENT involvement	1	44 (24)	12 (22.6)	30 (24)	0.032	38.9 (22.0)	41.8 (23.9)	0.046
Chondritis	2	2 (1.1)	1 (1.9)	1 (0.8)	0.094	3.3 (1.9)	1.3 (0.7)	0.1
Nasal crusts	2	12 (6.6)	3 (5.7)	9 (7.3)	0.065	9.3 (5.3)	13.5 (7.8)	0.102
Ocular involvement	2	12 (6.6)	3 (5.8)	8 (6.4)	0.026	12.6 (7.3)	10.4 (6)	0.053
Gastrointestinal tract involvement	2	18 (9.9)	9 (17.3)	9 (7.2)	0.312	34.3 (20.0)	13.2 (7.6)	0.366
Peripheral neuropathy	1	19 (10.4)	5 (9.4)	14 (11.2)	0.058	12.9 (7.3)	19.1 (10.9)	0.126
Mononeuritis multiplex		11 (6)	4 (7.5)	7 (5.6)		10.8 (6.1)	10.4 (5.9)	
Polyneuropathy		6 (3.3)	1 (1.9)	5 (4)		2.2 (1.2)	6.3 (3.6)	
Central nervous system	1	5 (2.7)	4 (7.5)	1 (0.8)	0.342	10.7 (6.0)	1.3 (0.7)	0.298
Cardiac involvement	0	15 (8.2)	5 (9.4)	9 (7.1)	0.083	21.3 (12.0)	12.2 (6.9)	0.174
Myocarditis		8 (4.3)	2 (3.8)	6 (4.8)		11.5 (6.5)	8.2 (4.6)	
Pericarditis		3 (1.6)	3 (5.7)	0 (0)		9.8 (5.5)	0 (0)	
BVAS[#]	29	21 [18,26]	22 [19, 27]	21.5 [20, 26]	0.055	21 [18, 26.77]	22 [19.44, 26]	0.116
SAPS II score[#]	21	42 [31,54.5]	42 [30, 52]	41 [31, 51]	0.017	41.33 [30, 52]	39.84 [31, 51]	0.042

Results are N (%), or medians (interquartile range); * Ambient air; FiO2: fraction of inspired oxygen; SpO2: peripheral capillary oxygen saturation; BAL: bronchoalveolar lavage; CT: Computed Tomography; RRT: renal replacement therapy; AKI: acute kidney injury; ENT: Otorhinolaryngology; BVAS: Birmingham Vasculitis Activity Score; SAPSII: simplified acute physiology score; Two-tailed p-values come from unadjusted comparisons using Chi square or Fisher's exact tests for categorical variables, and t-tests or Mann-Whitney tests for continuous variables, as appropriate. No adjustment for multiple comparisons was performed.

* Includes only patients who remained compatible with each arm by day 7 (not artificially censored).

[#] imputed using linear regression for censoring weights

Table 3. Treatment and ICU care of the 184 patients enrolled in the emulated trial, according to plasma exchange (PLEX) group, after cloning and censoring.

	Missing values	Whole sample (N=184)	Unweighted*			Weighted		
			No PLEX (N=53)	PLEX (N=126)	SMD	No PLEX (N=177)	PLEX (N=176)	SMD
Immunosuppressive agents								
IV cyclophosphamide	0	133 (72.3)	32 (60.4)	98 (77.8)	0.383	123.0 (69.2)	129.1 (73.2)	0.091
Oral cyclophosphamide	0	3 (1.6)	3 (5.7)	0 (0)	0.346	8.8 (4.9)	0 (0)	0.323
Rituximab	0	61 (33.2)	22 (41.5)	39 (31.0)	0.221	61.1 (34.6)	59.6 (33.9)	0.014
Glucocorticoid								
Pulses of methylprednisolone	0	176 (95.7)	48 (90.6)	124 (98.4)	0.349	171.2 (96.2)	171.4 (97.2)	0.058
Number of pulses	9	3 [3,3]	3 [3,3]	3 [3,3]	0.277	3 [3,3]	3 [3,3]	0.249
Dose of methylprednisolone pulses	11	750 [500,1000]	750 [500,1000]	660 [500,1000]	0.02	1000 [500,1000]	559 [500,1000]	0.144
Glucocorticoid regimen	21				0.113			0.079
PEXIVAS reduced dose		28 (17.2)	10 (20.4)	18 (16.2)		30.9 (18.7)	25.7 (16.6)	
PEXIVAS standard dose		86 (52.8)	25 (51.0)	58 (52.3)		78.5 (47.7)	79.8 (51.4)	
Other		49 (30.1)	14 (28.6)	35 (31.5)		55.2 (33.5)	49.7 (32)	
Management of organ failures								
High flow oxygen	0	85 (46.2)	23 (43.4)	61 (48.4)	0.101	75.2 (42.5)	85.4 (48.6)	0.122
NIV	1	37 (20.2)	11 (21.2)	25 (19.8)	0.033	32.8 (18.7)	36.3 (20.7)	0.049
Highest Fio2 (%)	27	66 [42,80]	60 [40,70]	66 [45,80]	0.171	60 [40,68]	66 [44,80]	0.147
NIV or HFO duration (days)	124	4 [2,6]	4.5 [2.75,5.5]	4 [2,6.5]	0.119	4 [2.08,5]	4 [2,6.86]	0.212
IMV	0	99 (53.8)	28 (52.8)	68 (54)	0.023	91.5 (51.8)	94.2 (53.6)	0.036
VAP	85	37 (37.4)	11 (37.9)	26 (37.7)	0.005	40.6 (43.8)	36.1 (37.8)	0.122
Neuromuscular blocking agents	85	72 (72.7)	19 (35.8)	50 (39.7)	0.079	61.8 (35)	68.7 (39.1)	0.085
Prone positioning	85	49 (49.5)	17 (32.1)	31 (24.8)	0.162	52.4 (29.6)	41.5 (23.8)	0.133
Inhaled nitric oxide	0	12 (6.5)	5 (9.4)	7 (5.6)	0.148	19.4 (11)	9.3 (5.3)	0.208

Veno-venous ECLS	0	16 (8.7)	3 (5.7)	12 (9.5)	0.146	8.3 (4.7)	15.3 (8.7)	0.16
Catecholamines	0	78 (42.4)	25 (47.2)	50 (39.7)	0.151	79.5 (44.9)	68.9 (39.2)	0.117
RRT	1	96 (52.5)	25 (47.2)	68 (54.4)	0.145	98.6 (55.8)	91.4 (52.3)	0.07

Results are N (%), or medians (interquartile range); PLEX: plasma exchange; IMV: invasive mechanical ventilation; VAP: ventilator acquired pneumonia; RRT: renal replacement therapy; NIV: non-invasive ventilation; IV: intra-venous; HFO: High flow oxygen; ECLS: extra-corporeal membrane oxygenation; Two-tailed p-values come from unadjusted comparisons using Chi square or Fisher's exact tests for categorical variables, and t-tests or Mann-Whitney tests for continuous variables, as appropriate. No adjustment for multiple comparisons was performed; Bolded p-values are significant at the $p<0.05$ level.

* Includes only patients who remained compatible with each arm by day 7 (not artificially censored).

Table 4. 30-day survival estimates and restricted mean survival time at 30 days.

	30 days survival, %	95% CI	HR	95% CI*	RMST (days)	95%CI
Original cohort (n=184) before emulation						
PLEX	83.95	(79.41; 88.49)	1.27	(0.48; 3.34)	27.87	(27.12; 28.61)
No PLEX	87.42	(80; 95.83)			27.97	(26.74; 29.45)
Difference	-3.48	(-12.98; 5.32)			-0.11	(-1.76; 1.48)
Emulated cohort						
PLEX	84.81	(80.15; 89.73)	1.27	(0.61; 3.95)	27.93	(27.19; 28.67)
No PLEX	87.97	(77.71; 95.91)			28.21	(26.64; 29.45)
Difference	-3.16	(-12.64; 7.51)			-0.29	(-1.66; 1.39)

HR: hazard ratio; CI: confidence interval; RMST: restricted mean survival time; PLEX: plasma exchange.

Table 5. Outcomes of the 184 patients enrolled in the emulated trial, according to plasma exchange (PLEX) group, after cloning and censoring.

	Missing values	Whole sample (N=184)	Unweighted*			Weighted		
			No PLEX (N=53)	PLEX (N=126)	SMD	No PLEX (N=177)	PLEX (N=176)	SMD
Alive at day 30	0	156(84.8)	47(88.7)	109(86.5)	0.066	156.4(88.4)	153.3(87.2)	0.039
Alive at day 90	16	128(76.2)	39(79.6)	89(78.1)	0.037	130.3(79.5)	126.2(79.2)	0.008
Alive at day 180	19	121(73.3)	38(79.2)	83(74.1)	0.12	128.2(79.3)	116.8(74.4)	0.116
Duration of hospital stay (days)	44	44[34,56]	46[27.5,60.5]	44[35,55]	0.017	42[28.52,60.66]	42.65[35,54.19]	0.164
ICU duration (days)	27	13[7,20]	13.50[6,25]	12[7,19]	0.108	13[6,25]	12[7,19]	0.163
IMV duration (days)	88	12[6,17]	12.50[6,18]	12[7,17]	0.174	11.96[6,18]	10[6,16.63]	0.162

Results are N (%), or medians (interquartile range); ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; Two-tailed p-values come from unadjusted comparisons using Chi square or Fisher's exact tests for categorical variables, and t-tests or Mann-Whitney tests for continuous variables, as appropriate. No adjustment for multiple comparisons was performed.

* Includes only patients who remained compatible with each arm by day 7 (not artificially censored).