

Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated Vasculitis (AAV)? PRO

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KIDNEY360 2: 776–778, 2021. doi: <https://doi.org/10.34067/KID.0006762020>

For decades, plasma exchange (PLEX) has been advocated for patients with rapidly progressive GN and diffuse alveolar hemorrhage due to ANCA (1–3). Autoantibodies in ANCA vasculitis are typically directed to one of two proteins, myeloperoxidase or proteinase-3 (PR3). These autoantibodies are pathogenic and trigger disease activity, activating primed neutrophils and monocytes, leading to vessel injury, and activation of the alternative complement pathway (4). PLEX can rapidly clear these pathogenic autoantibodies, potentially abolishing the inciting cause of ANCA vasculitis.

An early controlled study of PLEX for small-vessel vasculitis included 23 patients treated with standardized immunosuppression and 25 who received PLEX in addition (1). Among those who were dialysis dependent at presentation, 91% (10 out of 11) who received PLEX had improvement in kidney function at 1 month, compared with 38% (three out of eight) of those in the group who did not receive PLEX.

The subsequent Randomized Trial of Plasma Exchange or High-dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis (MEPEX) study included patients with ANCA vasculitis and severe renal failure, defined as a serum creatinine above 5.8 mg/dl (500 μ mol/L) randomized to receive PLEX or pulse intravenous (IV) methylprednisolone (5). A renal biopsy was required for inclusion. Among the 137 patients randomized, 67 received IV methylprednisolone and 70 received PLEX administered as a total of seven exchanges within 14 days of enrollment. The primary outcome was renal recovery at 3 months, defined as dialysis independence and serum creatinine <5.8 mg/dl (500 μ mol/L). At 3 months, 49% of the IV methylprednisolone group achieved renal recovery compared with 69% ($P=0.02$) of the PLEX group. At 12 months, each group had 51 surviving participants, and 59% (29 out of 51) in the IV methylprednisolone arm remained dialysis independent, compared with 80% (41 out of 51) who received PLEX ($P=0.008$). These findings remained statistically significant even in multivariable Cox regression analyses. Long-term follow-up of MEPEX evaluated outcomes in 120 patients who were initially enrolled and for whom vital status was available (6). Over a median of 3.95 years, the authors found no difference in a composite outcome of ESKD and death (hazard ratio [HR], 0.81;

95% confidence interval [95% CI], 0.53 to 1.23). Importantly, adverse events did not differ significantly between the two groups. When evaluating ESKD alone and accounting for death as a competing outcome, PLEX had a suggestion of benefit (HR, 0.64; 95% CI, 0.40 to 1.05; $P=0.08$) albeit not statistically significant. Some have argued this result should not be dismissed as clinically insignificant, because the original study was not designed for long-term outcomes and a substantial proportion of patients were lost to follow-up (7).

A meta-analysis that followed examined the benefit of PLEX in idiopathic rapidly progressive GN (8). Nine studies with 387 patients were included, using a composite outcome of ESKD and death. PLEX was associated with an improvement in the composite outcome (relative risk [RR], 0.80; 95% CI, 0.65 to 0.99; $P=0.04$). When examining ESKD alone, PLEX led to an approximate one-third reduction in risk (RR, 0.64; 95% CI, 0.47 to 0.88; $P=0.007$).

Szpirt *et al.* (9) enrolled 32 patients who had granulomatosis with polyangiitis in a single center in Denmark, and randomized them to receive PLEX in addition to cyclophosphamide induction or cyclophosphamide induction. Unlike MEPEX, they included patients over a wide range of kidney function. In the PLEX group, they used six sessions in total, administered every other day, but allowed for an additional three to six sessions if PR3 titers remained elevated. Over 5 years of follow-up, they noted improved renal outcomes in the PLEX group and in multivariable analysis reported that PLEX improved renal survival in patients with creatinine >2.85 mg/dl.

The American Society for Apheresis determined rapidly progressive GN with a creatinine ≥ 5.7 mg/dl to be a Category I (considered first-line therapy) indication for PLEX, but if creatinine was <5.7 mg/dl, the indication would be a Category III (optimal role not established) (3). Diffuse alveolar hemorrhage was determined also to be a Category I indication. The data to support the use of pulmonary hemorrhage in ANCA vasculitis have been somewhat limited. One retrospective series of 20 ANCA vasculitis patients from a single institution demonstrated resolution of pulmonary hemorrhage in all patients while receiving PLEX (2). In MEPEX, 31 patients had pulmonary hemorrhage—13 in the PLEX group and 18 in the IV methylprednisolone group; one

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patient died in the PLEX group and three in the IV methylprednisolone group (5). Another observational study from Japan in a large, inpatient sample identified 249 patients with ANCA vasculitis and pulmonary hemorrhage (10). Using propensity score matching, the authors compared 59 patients who received PLEX to 59 patients who did not, and demonstrated reduced overall in-hospital mortality (RR, 0.66; 95% CI, 0.43 to 0.99; $P=0.04$).

The Plasma Exchange and Glucocorticoids for Treatment of Antineutrophil Cytoplasm Antibody–Associated Vasculitis (PEXIVAS) study was published after much anticipation and is the largest study to date in ANCA vasculitis (11). PEXIVAS enrolled 704 patients with severe ANCA vasculitis (PR3 or myeloperoxidase positive), defined as renal injury with eGFR <50 ml/min per 1.73 m², and/or the presence of pulmonary hemorrhage. No benefit was observed with PLEX in reducing the primary composite outcome of ESKD or death.

As compared with MEPEX in which all patients had serum creatinine ≥ 5.8 mg/dl, fewer than one third (29%) of patients in PEXIVAS had this level of kidney injury. Additionally, PEXIVAS ascertained their composite outcome at any point in follow-up, which was a median of 2.9 years. Sensitivity analyses were performed at a truncated follow-up of 1 year, which also failed to demonstrate a benefit. However, examination of the Kaplan-Meier curve presented in the study for their composite outcome would suggest some early benefit that is lost over the longer follow-up period. In subgroup analyses of patients with severe kidney injury (creatinine >5.7 mg/dl), PLEX demonstrated a potential benefit on the primary outcome that did not reach statistical significance (HR, 0.77; 95% CI, 0.53 to 1.11) (11). These analyses did not examine the truncated 1-year follow-up period or any shorter period (as in the 3-month outcome in MEPEX), so the possibility of an early benefit to PLEX would not be captured. Examination of ESKD risk with death as a competing outcome rather than as part of a composite has also not been presented. Finally, 35 (10%) of the patients in the PLEX arm did not receive the prescribed number of treatments: 15 (4%) received none and 20 (6%) received between one and six PLEX treatments (11). Although PEXIVAS performed a “per-protocol analysis” ($N=338$), it remains unclear how these patients who are undertreated may have influenced the study results (12).

Another important criticism of PEXIVAS is the lack of presented kidney biopsy data. Kidney involvement could be defined by reduced kidney function with an active urine

sediment, but biopsy was not required (11). Most patients were new diagnoses, and patients with *documented* eGFR <50 ml/min per 1.73 m² for 3 months before enrollment were excluded. Because ANCA vasculitis may relapse and remit with episodic injury before a formal diagnosis is made, patients could present with severe kidney injury due to advanced sclerosis or due to acute inflammation (13). Those patients with advanced sclerosis would be much less likely to benefit from aggressive initial therapy. Indeed, in a retrospective cohort of patients with ANCA vasculitis and advanced kidney injury at presentation (median eGFR of 7.1 ml/min per 1.73 m²), Lee *et al.* (14) demonstrated that chronicity scoring of the kidney biopsy at presentation was an independent predictor of treatment response at 4 months. A kidney biopsy also is essential to exclude concomitant antglomerular basement membrane disease, which has been reported even when serologic testing is negative (15).

In PEXIVAS, 191 (27.1%) patients had some degree of lung hemorrhage—of these, 61 (32%) had severe hemorrhage defined as O₂ saturation $<85\%$, or need for mechanical ventilation. In subgroup analyses of these patients, there was again the impression of potential benefit for the composite outcome (HR, 0.64; 95% CI, 0.33 to 1.24 for less severe hemorrhage and HR, 0.67; 95% CI, 0.28 to 1.64 for severe hemorrhage) (11). Again, this outcome was the composite of either death or ESKD ascertained over the entire follow-up period. Any short-term benefit, benefit on death alone or on time to resolution of hemorrhage and improvement in lung function have not been presented.

Decisions to utilize PLEX in ANCA vasculitis should consider the totality of the data, including those preceding PEXIVAS. PLEX may afford short-term benefits in delaying ESKD, which could affect both quality of life and cost. Patients with life-threatening lung hemorrhage may also derive benefit from PLEX. Further, as none of the presented studies have demonstrated an excess of severe adverse events related to PLEX, the potential harm is likely low. An update to American Society of Apheresis guidelines following PEXIVAS had changed the indication for PLEX to a Category II for patients with creatinine ≥ 5.7 mg/dl, but cautiously stated this should not postpone use of PLEX (16). Lung hemorrhage remains a Category I indication, acknowledging the limitations in PEXIVAS. Until better therapies are available, PLEX should be considered in initial therapy for carefully selected patients with ANCA vasculitis (Figure 1), including those with severe acute inflammatory

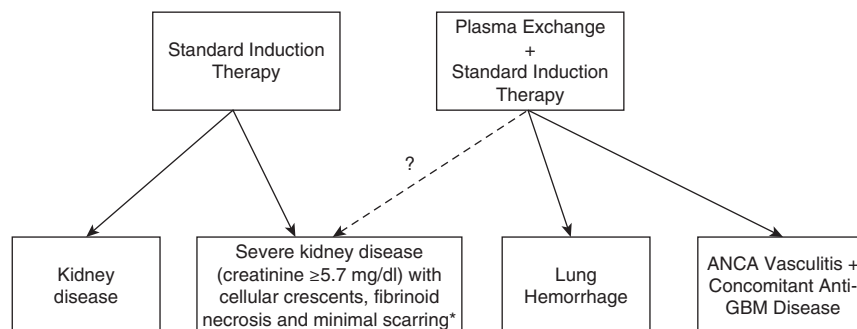


Figure 1. | A proposed schema for the use of plasma exchange in patients with ANCA vasculitis and renal and pulmonary disease. Anti-GBM disease, antglomerular basement antibody disease.

kidney injury and severe lung hemorrhage. Further, PLEX should remain a mainstay of therapy for those patients with ANCA vasculitis and persistent progressive disease, despite initiation of induction therapy, and for those with concomitant antiglomerular basement membrane disease.

Disclosures

V. Derebail has acted as a consultant for Bayer, Novartis, and Retrophin outside the submitted work.

Funding

V. Derebail was supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award numbers 5P01DK058335-20 (PI: Falk) and 1R01DK125350-01 (PI: Falk, Jennette, Free, Ciavatta).

Acknowledgments

The funding source had no role in study design, data collection, analysis, or interpretation, writing the report, or the decision to submit the report for publication. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

V.K. Derebail conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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Received: November 13, 2020 Accepted: November 30, 2020

See related debate, “Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated Vasculitis (AAV)? CON,” and commentary, “Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated vasculitis (AAV)? COMMENTARY,” on pages 779–781 and 782–783, respectively.