Should PLEX be used for severe AKI and/or pulmonary hemorrhage in patients with ANCA-associated vasculitis (AAV)? PRO

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For decades, plasma exchange (PLEX) has been advocated for patients with rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage due to anti-neutrophil cytoplasmic antibodies (ANCA).(1-3) Auto-antibodies in ANCA vasculitis are typically directed to one of two proteins, myeloperoxidase (MPO) or proteinase-3 (PR3). These auto-antibodies 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 auto-antibodies, 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% (10/11) who received plasma exchange had improvement in kidney function at one month compared to 38% (3/8) of those in the group who did not receive plasma exchange.

The subsequent MEPEX study included ANCA vasculitis patients with severe renal failure defined as a serum creatinine above 5.8 mg/dl (500 μmol/L) randomized to receive plasma exchange 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 μmol/L). At 3 months, 49% of the IV methylprednisolone group achieved renal recovery compared to 69% (p=0.02) of the PLEX group. At 12-months, each group had 51 surviving participants, and 59% (29/51) in the IV methylprednisolone arm remained dialysis independent compared to 80% (41/51) 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 initially enrolled patients for whom vital status was available. Over a median of 3.95 years, the authors found no difference in a composite outcome of end-stage kidney disease (ESKD) and death (HR 0.81, 95% CI 0.53-1.23). 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 – 1.05], p=0.08) albeit not statistically significant. Some have argued this result should not be dismissed as clinically insignificant since the original study was not designed for long-term outcomes and a substantial proportion of patients were lost to follow-up.

A meta-analysis that followed examined benefit of PLEX in idiopathic rapidly progressive glomerulonephritis. 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 (RR 0.80 [95% CI 0.65, 0.99], p=0.04). When examining ESKD alone, PLEX led to an approximate one-third reduction in risk (RR 0.64, [0.47-0.88], p=0.007).

Szpirt et al. enrolled 32 patients with granulomatosis with polyangiitis (GPA) 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 employed six sessions in total administered every other day but allowed for an additional 3-6 sessions if PR-3 titers remained elevated. Over five 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 glomerulonephritis with a creatinine ≥ 5.7 mg/dl to be a Category I (considered as first-line therapy) indication for PLEX, but if creatinine was <5.7 mg/dl, the indication would be a Category III (optimal role note 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 has 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; only 1 died in the PLEX group and 3 in the IV methylprednisolone group.(5) Another observational study from Japan in a large, inpatient sample identified 249 ANCA vasculitis patients with 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 0.43-0.99], p=0.04).

The Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA)-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 MPO-positive), defined as renal injury with estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m² and/or the presence of pulmonary hemorrhage. No benefit was observed with plasma exchange in reducing the primary composite outcome of end-stage kidney disease (ESKD) or death.
As compared to MEPEX in which all patients had serum creatinine $\geq 5.8$ mg/dl, fewer than one-third (29.1%) of PEXIVAS patients 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 one 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 sub-group analyses of patients with severe kidney injury (creatinine $>5.7$ mg/dl), PLEX demonstrated potential benefit on the primary outcome that did not reach statistical significance (HR 0.77 [95% confidence interval(CI) 0.53 – 1.11]).(11) These analyses did not examine the truncated one-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 1-6 PLEX treatments.(11) While PEXIVAS performed a “per-protocol analysis” (N=338), it remains unclear how these under-treated patients 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/1.73 m$^2$ for three months prior to 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 ANCA vasculitis patients with advanced kidney injury at presentation (median eGFR of 7.1 ml/min/1.73 m$^2$), Lee et al demonstrated that chronicity scoring of the kidney biopsy at presentation was an independent predictor of treatment response at 4 months.(14) A kidney biopsy also is essential to exclude concomitant anti-glomerular basement membrane (anti-GBM) disease which has been reported even when serologic testing is negative.(15)

In PEXIVAS, 191 (27.1%) patients had some degree of lung hemorrhage – 61 (31.9%) of these had severe hemorrhage defined as O$_2$ 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 0.33-1.24] for less severe hemorrhage and HR 0.67 [95% CI 0.28-1.64] 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 upon death alone or upon 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 impact 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 that 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 a carefully selected ANCA vasculitis patients (Figure 1) including those with severe acute inflammatory kidney injury and severe lung hemorrhage. Further, PLEX should remain as a mainstay of therapy for those with ANCA vasculitis patients with persistent progressive disease despite initiation of induction therapy and for those with concomitant anti-GBM disease.

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VKD: Conceptualization; Writing - original draft; Writing - review and editing
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Figure 1. A proposed schema for the use of plasma exchange in patients with ANCA Vasculitis with renal and pulmonary disease.
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Standard Induction Therapy: Corticosteroids + Cyclophosphamide or Corticosteroids + Rituximab
Anti-GBM Disease - anti-glomerular basement antibody disease

*Severe kidney disease (creatinine ≥5.7 mg/dl) with cellular crescents, fibrinoid necrosis and minimal scarring*

*Plasma exchange may have potential benefit in patients with severe, acute renal disease and minimal scarring but data for this are unclear.*