

Plasma Exchange in Patients With ANCA-Associated Vasculitis: A #NephJC Editorial on a comPLEX Question



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#NephJC is a recurring twitter-based journal club. #NephJC editorials highlight the discussed article and summarize key points from the NephJC TweetChat.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a devastating form of systemic vasculitis that can result in kidney failure, superadded infection, and death.¹⁻³ Plasma exchange (PLEX) for treating AAV was established based on biological plausibility and small clinical trials conducted in the 1980s-1990s. Its role was further cemented in 2007 when Jayne et al⁴ recruited 137 patients with severe AAV (serum creatinine >500 $\mu\text{mol/L}$ [5.7 mg/dL]) and demonstrated higher rates of independence from dialysis at 3 months for those who received PLEX compared to those who received induction with intravenous methylprednisolone (MEPEX). However, long-term follow-up at 4 years did not demonstrate benefit for either mortality or kidney survival.⁵

Thirteen years later, the PEXIVAS (Plasma exchange and glucocorticoid dosing in the treatment of antineutrophil cytoplasm antibody-associated vasculitis) trial challenged the role of routine PLEX use in AAV with kidney or pulmonary involvement. The largest randomized controlled trial of AAV to date, PEXIVAS enrolled an impressive 704 patients with AAV and estimated glomerular filtration rate <50 mL/min/1.73 m² (including those needing dialysis) or pulmonary alveolar hemorrhage (PAH) to PLEX vs No-PLEX. There was no benefit of PLEX on the primary composite outcome of death or kidney failure (kidney failure hazard ratio, 0.86; 95% CI, 0.65-1.13) after a median follow-up of 2.9 years.⁶

The risks associated with PLEX now needed to be balanced against a seemingly diminishing benefit; it is pertinent to note the different inclusion criteria for renal function in the 2 prominent trials. The stage was set for the PEXIVAS authors to undertake an updated meta-analysis to see what the entirety of the evidence tells us.

The Study

This updated systematic review and meta-analysis included randomized controlled trials that enrolled adult patients with AAV where PLEX was used in addition to other induction immunosuppressive therapies. Outcomes, considered at or after 12 months, were at least one of the

following: mortality, kidney failure, serious infection (needing hospitalization or intravenous antibiotics), disease relapse, serious adverse events, or change in health-related quality of life. The risk of bias was assessed using the Cochrane tool, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess certainty of evidence. The authors evaluated subgroup effects based on baseline kidney function, comparing those with a serum creatinine (SCr) of ≥ 500 $\mu\text{mol/L}$ or on dialysis, to those with SCr <500 $\mu\text{mol/L}$. Absolute risk reductions were calculated across a range of baseline risks, which were divided into 4 groups: low risk (SCr ≤ 200 $\mu\text{mol/L}$), low-moderate risk (SCr >200-300 $\mu\text{mol/L}$), moderate-high risk (SCr >300-500 $\mu\text{mol/L}$) and high risk (SCr ≥ 500 $\mu\text{mol/L}$ or on dialysis).⁷

Nine randomized controlled trials were included in this review, which incorporated data from 1,060 patients with a median follow-up of 3 years. These included smaller trials from the 1980s-1990s, the MEPEX trial and its long-term follow-up results, long-term results from the trial conducted by Szpirt et al,⁸ as well as the recent PEXIVAS trial.⁴⁻⁶ The length of follow-up varied from 12 months to 127 months. The authors conducted the analysis at a 12 month end point because it is commonly reported in the included studies and the timeframe is short enough to reflect the acute nature of PLEX and long enough to capture a large proportion of events. Overall, PLEX had little or no effect on mortality, neither at 12 months (relative risk [RR], 0.9; 95% CI, 0.64-1.27; moderate certainty) nor at longer term follow-up (RR, 0.93; 95% CI, 0.73-1.19; moderate certainty). There was also no evidence of subgroup effect by baseline kidney function or PAH. However, PLEX did reduce the risk of persistent kidney failure requiring dialysis at 12 months (RR, 0.62; 95% CI, 0.39-0.98) and may have affected longer-term risk (RR, 0.79; 95% CI, 0.58-1.08; low certainty), with no subgroup effect based on kidney function. The estimated absolute risk reduction in kidney failure requiring dialysis for PLEX was higher for those at highest risk (16%, 4.2%-23.6%, high certainty of important effects) compared to those at lowest risk (0.08%, 0.02%-0.12%, high certainty of no important effects). Additionally, PLEX was associated with an increased risk of serious infection at 12 months (RR, 1.27; 95% CI, 1.08-1.49; moderate certainty) and possibly at longer-term follow-up (RR, 1.13; 95% CI, 1.03-1.24; low certainty). Once again, the increased infection risk

(estimated absolute risk) was greatest in the same group who were at highest risk of kidney failure (13.5%) and lowest for those at lowest risk of kidney failure (2.7%). PLEX had little or no effect on the other outcomes including other serious adverse events, relapse, or health-related quality of life.

The TweetChat

The NephJC Twitter discussions on this meta-analysis on April 5, 2022 and April 6, 2022 included a combined 200 participants and 923 tweets. As expected, any discussion of PLEX for AAV allowed participants to rehash original criticisms of the PEXIVAS trial. Recommending PLEX without a kidney biopsy is widely debated and was seen by some as a limitation in the PEXIVAS trial. Even if positive immunology in the right clinical scenario is accepted as sufficient to diagnose AAV, some felt the additional information about activity and chronicity on kidney biopsy is key in guiding their decision making. In PEXIVAS and other trials, this was a pragmatic decision. It was also evident from the Tweetchat that the histological scoring systems for AAV (Brix score, Mayo Clinic, or Berden classification) are not actually used widely, and it was suggested that they may help in decision making.

The results of the present meta-analysis persuaded both Go-PLEX and No-PLEX groups. The trump card for team Go-PLEX was that PLEX reduced the risk of persistent

kidney failure requiring dialysis 12 months. Avoiding dialysis, even for a few months, is valuable for both patients and clinicians. The impact on health-related quality of life was surprisingly unchanged by PLEX, though this data point was obtained exclusively from PEXIVAS. Whether this reflects the burden of residual chronic kidney disease or the complications from ongoing immunosuppressive treatments was the subject of much discussion. Many chat participants discussed the seemingly discordant results of MEPEX and preceding trials compared with PEXIVAS. However, the initial benefit was no longer apparent in the longer-term follow-up study of the MEPEX cohort,⁵ similar to the PEXIVAS results.⁶

In this meta-analysis, PLEX for AAV did not have any effect on all-cause mortality, irrespective of the presence or absence of PAH. For most of the chat participants, this was no surprise, probably because of the pessimistic post-PEXIVAS atmosphere. The chat participants deliberated over the risk of serious infectious complications, particularly in high-risk patients. To reduce the risk of infections, participants pondered on the use of prophylaxis, eg, adding trimethoprim/sulfamethoxazole. Team No-PLEX held position here; increased infection risk without decreased mortality was hard to justify.

Decision making around the use of PLEX in AAV for short-term freedom from dialysis, with the paucity of longer-term benefit from persistent kidney failure or

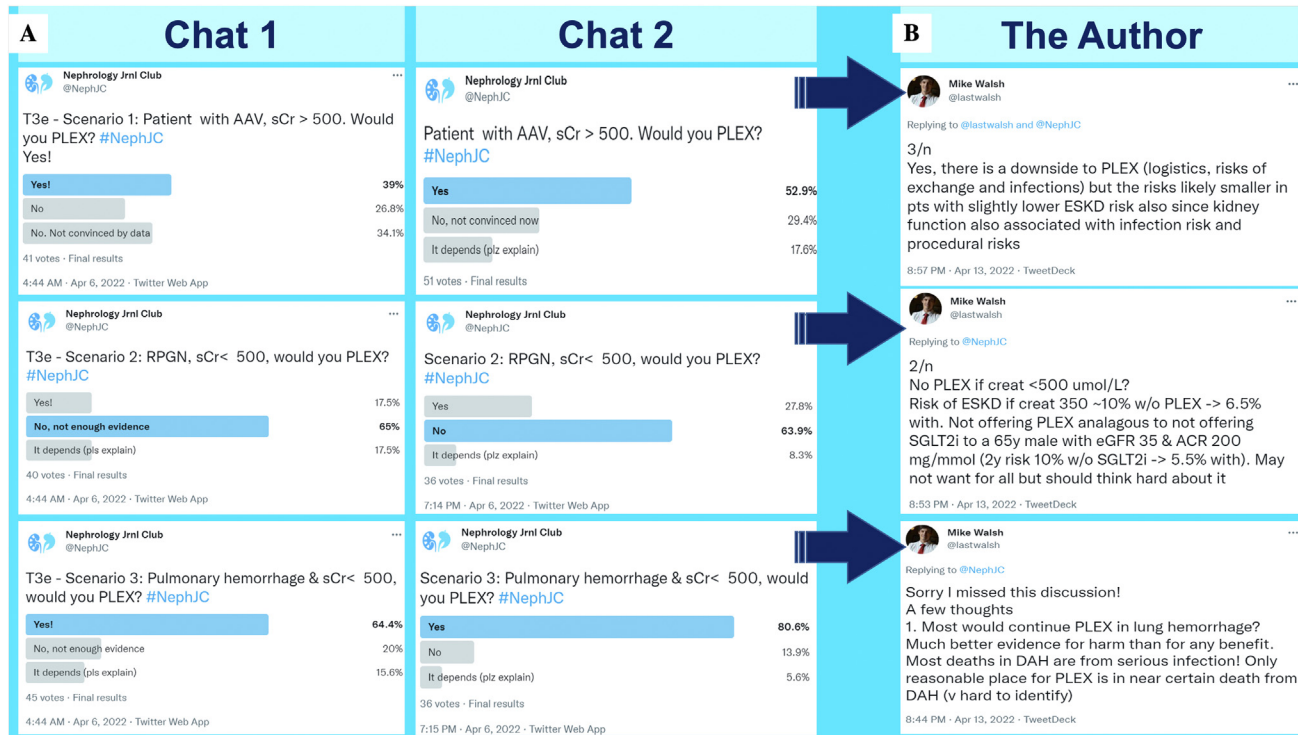


Figure 1. (A) Twitter polls from the start of the 2 Tweetchats depicting various clinical scenarios when PLEX could be used. (B) The author's response to the Twitter polls, clarifying and adding context why the crowd-sourced polling result was wrong. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; DAH, diffuse alveolar hemorrhage; ESKD, end-stage kidney disease; PLEX, plasma exchange; RPGN, rapidly progressive glomerulonephritis; SCr, serum creatinine; SGLT2i, sodium/glucose cotransporter 2 inhibitor.

death, coupled with a higher infection risk, remains complex. Overall there seemed to be a cautious resurgence of enthusiasm toward using PLEX in AAV. Chat participants responded to 3 polls, illustrating different case scenarios and PLEX indications (Fig 1A). For both chats, participants were in favor of PLEX in the setting of PAH and when creatinine was $>500 \mu\text{mol/L}$, but not when it was $<500 \mu\text{mol/L}$. It was also noted that the “500 $\mu\text{mol/L}$ ” threshold chosen was an artificial dichotomy in the setting of rapidly progressive glomerulonephritis when creatinine may increase daily, and a lower creatinine often signifies earlier recognition rather than less severe disease. Most interestingly, the principal author chimed in (Fig 1B), persuasively arguing against the “wisdom of the crowd.” For instance, he pointed out that in the setting of PAH, the higher mortality is most commonly driven from infection, which is increased by the use of PLEX.⁹

If PEXIVAS was considered a medical reversal to stop using PLEX in AAV, this meta-analysis might allow PLEX to bounce back. Before and during the Tweetchat discussion, the same clinical scenario about employing PLEX in the setting of AAV with creatinine $>500 \mu\text{mol/L}$ was proposed and elicited different responses. In the end, a larger proportion of participants were not so categorically No-PLEX, maybe inclining to particularize the PLEX decision for every case. For additional context, the author also suggested there is a nuanced position (Fig 1B). The decision for PLEX should be shared with the patient, explaining the risks and benefits associated with it, especially when rapidly progressive glomerulonephritis is present.

Conclusion

Before the meta-analysis, team Go-PLEX felt validated by MEPEX, and team No-PLEX felt validated by PEXIVAS. This meta-analysis tried to find a balance, and the key message from the Tweetchat was to individualize the decision for each patient with AAV.

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