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Perspective

Should We Still Use Therapeutic Plasma Exchange for Rapidly Progressive Glomerulonephritis in ANCA Associated Vasculitis?

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Abstract: For over thirty-five years, available data suggested that therapeutic plasma exchange (TPE) was a useful treatment for patients with Rapidly Progressive Glomerulonephritis (RPGN) associated with ANCA Associated Vasculitis (AAV) and elevated creatinine levels. The publication of the PEXIVAS study has challenged this conclusion. This perspective will outline the history of this issue and present our assessment of the current status.

Keywords: therapeutic plasma exchange; PLEX; RPGN; ANCA; PEXIVAS

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1. Introduction

This paper has been prepared to comment on the most recent metanalysis published since the PEXIVAS trial results on TPE in AAV [1]. The paper by Walsh et al. is based on nine trials and 1060 AAV patients. As with PEXIVAS, the authors did not find any effect of TPE on all-cause mortality (relative risk 0.90 (95% CI 0.64 to 1.27) [2]. However, data from seven trials involving 999 participants that included ESKD (End stage kidney disease) as an end-point demonstrated that TPE did reduce the risk of ESKD at 12 months (relative risk 0.62 (0.39 to 0.98)). Of concern, however, are data from four trials including 908 participants that showed that TPE increased the risk of serious infections at 12 months (relative risk 1.27 (1.08 to 1.49)). This last finding has not been previously reported as a major concern and we will address this issue further on in this paper.

2. Mechanism of Benefit of TPE

A cogent discussion of the possible benefit of TPE for the treatment of AAV RPGN should consider the mechanism of this benefit. The natural half-life of IgG antibodies is 21 days [3–5], assuming that immunosuppressive medication (ISM) can completely inhibit new antibody production, it would take up to 4 half-lives (84 days) for existing autoimmune antibodies to decline by 94%. (Figure 1). In contrast, 5 to 8 TPE treatments performed over a 2-week period can lower pre-exiting antibodies by more than 90% (Figure 1). Thus, the use of TPE in patients with AAV RPGN results in a rapid lowering of the preexisting pathogenic antibodies, thus avoiding 2 to 3 months of ongoing antibody mediated renal damage until immunosuppressive medication (ISM) is effective. Furthermore, the French Vasculitis Study Group (FVSG) just initiated the CINEVAS study to compare auto-antibody removal kinetics between PLEX and Immunoadsorption (IAS) in AAV and anti-GBM disease (personal communication Noème Jourde-Chiche) which could determine if IAS is a more effective modality.

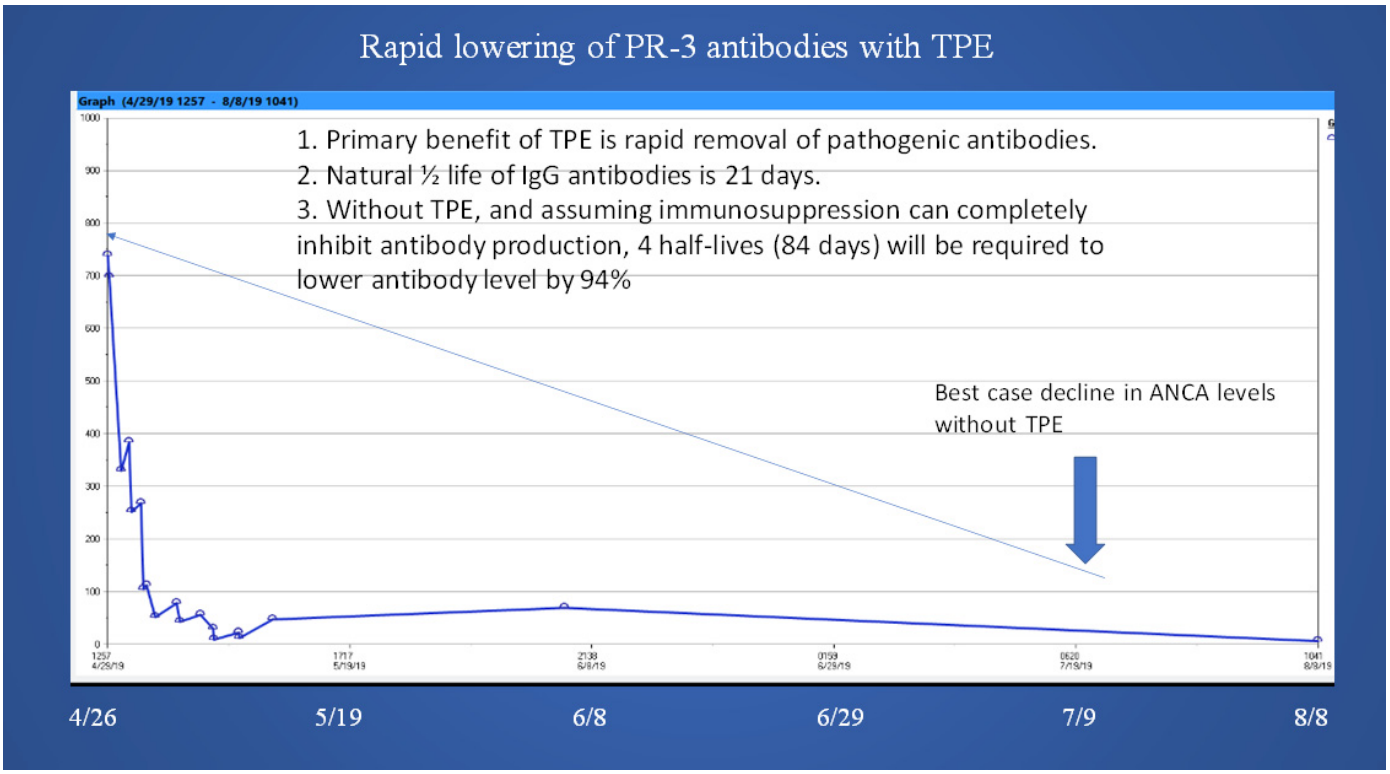

Figure 1. Rapid lowering of PR-3 antibodies with TPE.

3. Are ANCA Pathogenic?

The next issue is whether ANCA are pathogenic or are they simply diagnostic markers of the disease. In the case of AAV there appears to be convincing evidence that ANCA are pathogenic and capable of creating tissue damage (Lionaki and Falk) [6] and that ANCA are capable of activating leukocytes in vitro (Falk and Jennette) [7]. In animals, anti-myeloperoxidase antibodies were found to induce necrotizing GN and vasculitis (Xiao et al.) [8] and there has even been a case of transplacental transfer of ANCA resulting in vasculitis in a newborn infant (Schlieben et al.) [9] This case describes a mother with reactivation of MPA during pregnancy. In another case, transplacental transfer of ANCA did not result in active disease in the infant (Silva et al.) [10]. This mother had been on azathioprine maintenance therapy and in remission with elevated MPO-ANCA levels prior to her pregnancy. Given the potential of dissimilar outcomes associated with the presence of ANCA antibodies it would appear that ANCA are more likely to be associated with active vasculitis when there is a concurrent inflammatory milieu as may occur with cytokine release or activation of the complement cascade. Thus, available evidence suggests that ANCA *can* be pathogenic leading to a reasonable conclusion that the rapid lowering of these antibodies would benefit the outcome of ANCA associated tissue damage. Furthermore, complement activation via the alternative pathway is a part of the pathogenesis of AAV (Xiao and Schreiber) [11] and TPE may be able to remove the activated complement factors.

4. Results of Clinical Trials

Given this mechanistic argument of why TPE may benefit patients with AAV RPGN, the next issue is to review the evidence of benefit in clinical trials. Early attempts to treat RPGN with TPE predated the identification of ANCA and treatment trials were performed on patients who presented with "idiopathic RPGN". This designation was reserved for those patients whose biopsies were negative for anti-GBM and a variety of other, well-defined immune complex deposition diseases, such as SLE, IgA Nephritis or cryoglobulinemia. (the term "idiopathic RPGN" was used *before* the identification of ANCA antibodies, thus these were *not ANCA negative* patients). With the identification

of ANCA, the majority of patients with RPGN could be definitively classified as having ANCA associated disease or not.

In a retrospective study of 889 cases of RPGN, Jayne et al. [12] reported that 47 (5%) were positive only for anti-GBM antibodies, 246 (28%) were positive only for ANCA and 20 (2%) had both, while 576 (65%) had neither and probably had one of the systemic diseases listed above (SLE, IgA, cryoglobulinemia, etc.). Considering the current ability to classify these nephritides, the previous studies evaluating the potential benefit of TPE for "idiopathic RPGN" are difficult to evaluate with definitive accuracy. In any event, since most "pauci-immune glomerulonephritides" are *now known* to be ANCA-associated, one might extrapolate the available data accordingly.

Despite favorable uncontrolled reports [13–15] the results of four randomized, controlled studies failed to demonstrate a generalized benefit for TPE in the treatment of "idiopathic RPGN" when added to standard immunosuppressive therapy [16–19]. Nonetheless, a post hoc subset analysis of these studies suggested that TPE could be beneficial for those patients presenting with severe disease or dialysis dependency [20]. In one study in which this issue was specifically addressed, Pusey et al. [18] randomized 48 patients with crescentic GN in whom anti-GBM disease and immune complex mediated disease was excluded. Although patients were not tested for ANCA, the clinical diagnoses were that of Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA), Renal Limited Vasculitis (RLV), and idiopathic RPGN. In 25 patients, TPE was initiated with five 4-Litre exchanges in the first week with a subsequent mean total of 9 treatments per patient (range 5–25)). Immunosuppressive treatment with prednisolone, cyclophosphamide and azathioprine was administered to all 48 patients. Results revealed no outcome difference in those patients in whom treatment was initiated when serum creatinine was less than 500 μmol/L (<5.7 mg/dL). Of those patients who were originally dialysis dependent, however, 10 of 11 receiving TPE recovered renal function, while only 3 of 8 in the non-TPE group recovered to a similar degree ($p = 0.04$).

Subsequently, Jayne et al., 2007 [21] reported the results of the MEPEX Study. This trial randomized patients to receive TPE or one-gram i.v. pulses of methylprednisolone (MPP) delivered daily on 3 consecutive days as adjunctive therapy for severe renal vasculitis. In total, 137 patients with a new diagnosis of AAV RPGN with serum creatinine > 500 μmol/L (5.7 mg/dL) were randomized in the MEPEX trial. Both groups received oral cyclophosphamide and oral prednisolone. Overall, 70 patients received 7 TPE treatments, whereas 67 received MPP. At 3 months, 49% of those patients who were given MPP without TPE were alive and independent of dialysis, while 69% of those undergoing TPE were alive and off dialysis (95% CI 18 to 35%; $p = 0.02$). At 12 months, the risk of ESKD was 19% after TPE, and 43% after MPP (95% CI 6.1 to 41%). Patient survival and severe adverse event rates were similar in both groups. This study confirmed the beneficial effect of TPE on the rate of renal recovery of AAV RPGN in patients who presented with advanced renal failure when compared to MPP.

In a follow-up study published in 2011, Walsh et al. [22] performed a meta-analysis of nine studies involving 387 patients with renal vasculitis who were randomized to receive TPE or not and concluded that those receiving TPE had improved renal survival.

A reasonable question would be why the benefit of TPE seemed to be limited to those patients with substantial decline in renal function or those already on dialysis. If one considers that these patients had already shown evidence of significant renal damage, one could conclude that these were patients in whom the slow, natural decline in levels of pathogenic ANCA was too slow a process to protect them from ongoing irreversible renal damage, thus the benefit of TPE in rapidly lowering the level of these antibodies. Finally, in 2011, a RCT by Szpirt et al. [23] demonstrated short and long-term effects of PLEX in GPA patients with creatinine values of 250 μmol/L (2.85 mg/dL).

Thus, as of 2011 the available data involving more than 387 patients supported the use of TPE for ANCA patients with significant renal involvement. It was in the context of the above experience that the results of PEXIVAS were reported in 2020. PEXIVAS was the

largest, prospective, randomized study of TPE for AAV. The study evaluated 704 patients with newly diagnosed or relapsing GPA or MPA induced with standard therapy with cyclophosphamide or rituximab and randomized to adjunctive TPE or not. In a subset analysis, the outcome of 205 patients with creatinine > 500 μmol/L (5.7 mg/dL) was analyzed revealing no long-term benefit in the TPE group. In an accompanying editorial, however, Vimal and Falk [24] concluded that the trial may have been limited because of a lack of renal biopsy data at the inclusion with a possible bias between the groups. The editorial opined that patients with advanced renal dysfunction may have had active inflammation which might respond to TPE as opposed to more chronic sclerosis and fibrosis which would not respond. Of note is that most of the renal biopsies have since been collected among the participating 104 centers and will be the subject of an ancillary post PEXIVAS study. In the MEPEX study renal biopsies were evaluated for all patients enrolled.

Subsequently, in the March 2022 edition of JASN, Nezam et al. (FVSG) [25] published a prediction model where kidney histopathology findings could estimate influence of PLEX on mortality or ESKD at 12 months. The model was based on retrospective data of a nationwide French cohort of 425 AAV patients where 188 were treated with PLEX. The better prognosis factors found were in the subset of patients having MPA, MPO-ANCA positivity, higher serum creatinine, crescentic and sclerotic biopsy Berden classes, and higher Brix scores. The absolute risk reduction for death or ESKD at 12 months was 24.6%. These findings were criticized by Moura et al. [26] who did not agree with the conclusions of Nezam et al. as the response to PLEX was not different between the analyzed PLEX group and the control group but rather reflected the risk factors for the outcomes at 12 months. Thus, these findings must be validated before utilized in clinical decision making.

PEXIVAS randomized a total of 704 patients but only 205 of these patients had elevated creatinine > 500 μmol/L (5.7 mg/dL) or on dialysis. These patients were the only patients who were in a group in which previous trials had concluded were most likely to benefit from TPE. Despite clear separation on the outcome data (Figure 2) there is no statistical assessment at 3 months. At 1 year, no statistical benefit was noted but the outcome data are diluted with most patients having creatinine < 500 μmol/L (5.7 mg/dL) or DAH (diffuse alveolar hemorrhage) and no biopsy data were provided. Why should PEXIVAS results negate the MEPEX results?

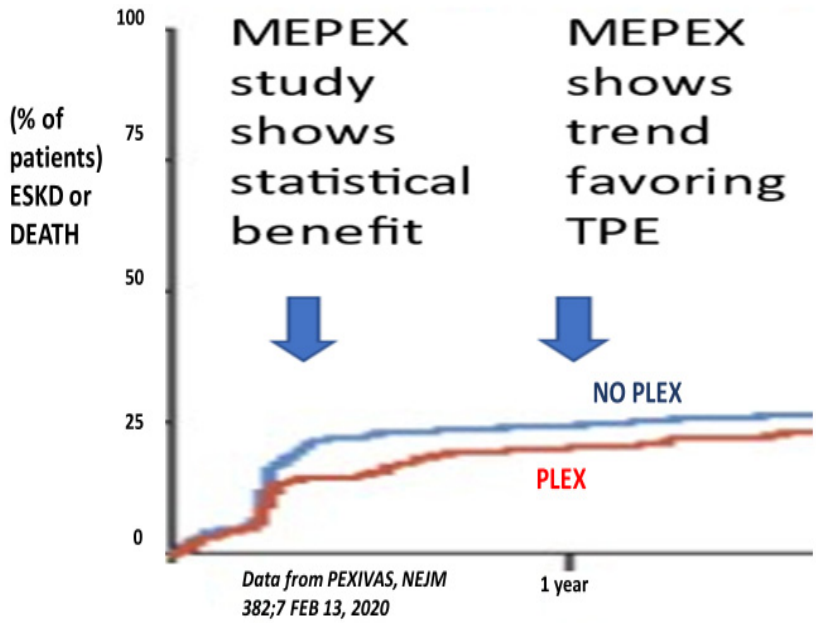

Figure 2. Primary outcome for the first year according to plasma exchange. Data from Walsh M, Merkel PA, Peh CA et al. Plasma exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis (PEXIVAS). NEJM 2020; 382:622 [1].

Further concerns regarding the PEXIVAS results were raised during subsequent evaluation of the study [27]. Authors were asked how many patients did not receive all seven TPE treatments? The authors response: Of 317 patients in the TPE group: 20 (6%) received between one and six exchanges and 15 (4%) received no exchanges. Thus: 35/317 = 11% of patients in the TPE group did not receive the full dose of TPE. Of potentially greater concern is that there were only 101 patients in the renal failure group with high creatinine > 500 µmol/L (5.7 mg/dL) or on dialysis who were in the TPE treated group. We do not know how many of these patients had reduced number of TPE treatments. It is possible that up to 35 pts in the TPE group who had creatinine greater than 500 µmol/L (5.7 mg/dL), or were on dialysis, did not receive the full dose of TPE, the group previously identified as most likely to respond.

Another issue of interest is the apparent improvement in the outcome of the TPE treated group after 3 months (Figure 2). This improvement is ignored in the manuscript and no statistical assessment was offered. It is of note that an improved renal survival at 3 months was noted in TPE treated patients in the MEPEX study yet this concurrence within the PEXIVAS outcome was not mentioned. It may be that being off dialysis within the first 3 months of treatment may not have been of significance, but one would not be surprised if the patients themselves would have greatly appreciated the "dialysis holiday" that may have lasted for up to a year. Furthermore, when M. Walsh presented PEXIVAS at the April 2022 ANCA workshop in Dublin, he referred to a patient survey where the patients did not support receiving plasma exchange regardless of the possibility of decreasing time on dialysis. The only documentation on this subject we found was in Zeng's et al. recommendations [28] where the authors specified that 20 patients participated in the survey and responses were discussed by a panel of four patient partners with ANCA-associated vasculitis with or without experience of plasma exchange and a caregiver for a patient who had end stage kidney disease. Based on the survey and panel discussion, the panel agreed that, for patients with low or low-moderate risk of developing ESKD, the harm of serious infections outweighed the benefits in terms of reduction in ESKD; but, because it was a close balance, the majority of patients but not all (50–90%) would decline plasma exchange. Finally, the panel agreed that, for patients with moderate-high or high risk of developing ESKD or requiring dialysis, the benefits outweigh the harms, such that the majority of patients would choose plasma exchange.

5. Cost Analysis of Providing TPE

Finally, one must consider the costs of TPE. Currently, the cost of TPE in the United States is approximately USD 2000 per treatment. Assuming a total of seven TPE treatments for a patient with AAV RPGN, the cost of these treatments would be USD 14,000 per patient. In contrast, according to the USRDS (2018) [29], the cost of 1 year of hemodialysis for ESKD is USD 90,000. If a patient with ESKD would survive on dialysis for one year, the cost of the seven TPE treatments compared to the cost of chronic hemodialysis for one year would be USD 14,000/90,000 = 0.16. Thus, one could conclude that if only 16% of all TPE treated patients avoided dialysis for 1 year, the cost of providing TPE to all AAV RPGN patients will be equal to the cost of not providing TPE. If one considers that the MEPEX trial found that those patients undergoing TPE had an 81% chance of being off dialysis in 12 months, the monetary outlay for providing the TPE treatments would be very cost effective.

6. Risk of Serious Infection with TPE

In regard to the unanticipated increase in serious infections in TPE treated patients as concluded by the most recent meta-analysis [2], a previous review involving over 5000 treatments in eight studies did not find an increased risk of serious infections in patients undergoing TPE [30]. In a most convincing report, a prospective, randomized study of 86 patients undergoing treatment for Lupus nephritis found no increased risk of serious infection in patients undergoing TPE when compared to those receiving only immunosuppressive medications (Pohl et al.) [31]. Of note, however, is that the immuno-

suppressive treatment given to both groups was limited to cyclophosphamide and steroids. Given the current use of rituximab as a common addition to immunosuppressive treatment for ANCA associated RPGN and given the substantial and prolonged immunosuppressive action of rituximab, it may be wise to replace some of the immunoglobulins which would undoubtedly be removed by TPE treatments. A reasonable approach would be to replace immunoglobulin levels with a single infusion of immunoglobulin of 100 to 400 mg/kg at the end of the last TPE treatment. The use of lower doses of glucocorticoids may also lower the risk of infections as suggested by the PEXIVAS results.

7. Conclusions

Studies prior to PEXIVAS showed benefit for TPE in patients with advanced renal disease ((creatinine $\geq$ 500 μmol/L (5.7 mg/dL) or requiring dialysis)). PEXIVAS randomized only 205 with advanced renal disease and found no benefit for TPE in these patients. Hopefully, the ongoing assessment of renal biopsies from the PEXIVAS patients will allow further insights into the lack of benefit in the TPE treated patients. Furthermore, 35 patients in PE group did not receive the prescribed full dose of TPE. The effect of these undertreated patients is unknown and may be very significant if a substantial number of these undertreated patients were in the group of 101 patients with creatinine $\geq$ 500 μmol/L (5.7 mg/dL) or those on dialysis, the group most likely to benefit from TPE. Finally, the cost of providing TPE with possible benefit may be less than the costs of chronic dialysis if no TPE is provided. It is then reasonable to conclude that the PEXIVAS data on its own is not sufficient to negate previous recommendations that TPE may benefit ANCA patients with advanced renal disease. The new meta-analysis on AAV RPGN, with inclusion of the PEXIVAS patients, recommends TPE in patients with serum creatinine > 300 μmol/L (3.42 mg/dL). We propose that TPE should be considered in addition to immunosuppression in those patients presenting with rapid decline in renal function independent of the absolute creatinine values. Hopefully, the ongoing evaluation of the renal biopsies at admission of the PEXIVAS patients will offer further insights into the potential benefit of TPE in AAV RPGN.

P.S.

To provide an update on the issue of PLEX for active renal disease in AAV, we report that during the EULAR 2022 Congress in Copenhagen 1–4 June the EULAR recommendation on AAV treatment concluded that "PLEX may be considered as a part of therapy in GPA/MPA for those with a serum creatinine > 300 μmol/L (3.42 mg/dL) due to active glomerulonephritis". The present survey on AAV treatment, including use of PLEX, by Duvuru Geetha and Tingting Li, Baltimore/St Louis, will possibly report if the "vasculitis" community is still using plasma exchange despite the PEXIVAS findings. (submitted to ASN/ACR 2022).

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