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PLEX in AAV-GN: insights from the meta-analysis results and impact on remission induction treatment recommendations

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ABSTRACT

The risk of progression to end-stage kidney disease (ESKD) in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and glomerulonephritis (AAV-GN) remains high. At 5 years of follow-up, 14–25% of patients will evolve to ESKD, suggesting that kidney survival is not optimized in patients with AAV. The addition of plasma exchange (PLEX) to standard remission induction has been the standard of care, particularly in patients with severe renal disease. However, there is still some debate regarding which patients benefit from PLEX.

A recently published meta-analysis concluded that the addition of PLEX to standard remission induction in AAV probably reduced the risk of ESKD at 12 months and that PLEX was associated with an estimated absolute risk reduction for ESKD at 12 months of 16.0% for those at high risk or with a serum creatinine >5.7 mg/dl (high certainty of important effects). These findings were interpreted as supportive of offering PLEX to patients with AAV and a high risk of progression to ESKD or requiring dialysis and are making their way into societies recommendations.

However, the results of the analysis can be debated. We provide an overview on the meta-analysis as an attempt to guide the audience through how the data were generated, to comment on our interpretation of the results and to explain why we feel uncertainty remains. In addition, we would like to provide insights in two questions that we believe are very relevant to consider when addressing the role of PLEX: the role of kidney biopsy findings in the decision making of whom might benefit from PLEX and the impact of novel treatments (i.e. complement factor 5a inhibitors) in avoiding progression to ESKD at 12 months. The treatment of patients with severe AAV-GN is complex and further studies that include only patients at high risk of progression to ESKD are needed.

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LAY SUMMARY

The article reviews the evidence on the use of plasma exchange (removal of the patient's own plasma in exchange for normal saline and albumin) in the treatment of severe antineutrophil cytoplasmic antibody–associated vasculitis. It points out that depending on the type of study or if the study was done many years ago versus more recent studies that incorporate modern care, the conclusions about its efficacy can change. It also discusses that the decision regarding its use should not be based solely on the level of kidney function at the time of diagnosis. The arrival of new medications to treat this type of vasculitis may make discussions on whether to use plasma exchange irrelevant.

Keywords: ANCA, crescentic glomerulonephritis, plasma exchange, rituximab, vasculitis

The use of plasma exchange (PLEX) for the treatment of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with active glomerulonephritis (AAV-GN) has been a matter of debate, particularly since the publication of the Methylprednisolone versus Plasma Exchange (MEPEX) trial in 2007 [1]. In this trial, conducted between March 1995 and October 2002, the authors compared the addition of PLEX or methylprednisolone (70 versus 67 patients) to a cyclophosphamide-based remission induction treatment for patients with severe kidney disease [serum creatinine (SCr) >5.8 mg/dl]. The study concluded that the use of PLEX was of benefit to avoid the progression to end-stage kidney disease (ESKD) by 12 months {hazard ratio [HR] 0.47 [95% confidence interval (CI) 0.24–0.91]; $P = .03$} [1], but the effect was lost soon afterwards [2]. Thereafter the use of PLEX in addition to standard remission induction therapy became a widely accepted practice for patients with AAV and severe kidney involvement. In 2011, a meta-analysis of nine randomized clinical trials (356 patients) that evaluated the progression to ESKD at any time point showed that patients who received PLEX had improved kidney survival [relative risk (RR) 0.64 (95% CI 0.47–0.88); $P = .006$], but the statistical information was considered insufficient to reliably determine whether PLEX could decrease the composite of ESKD or death [3]. To further clarify this question, the Plasma Exchange and Glucocorticoids for Treatment of ANCA-Associated Vasculitis (PEXIVAS) trial was conducted. The study enrolled 704 patients and showed no benefit of adding PLEX to standard remission induction therapy in patients with an estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m^2 [HR 0.86 (95% CI 0.65–1.13); $P = .27$] [4]. Similarly, no benefit was shown in the subanalysis of patients with SCr >5.6 mg/dl versus ≤5.6 mg/dl [HR 0.77 (95% CI 0.53–1.11)] [4].

Recently Walsh *et al.* [5] conducted a systematic review of all nine randomized controlled trials published by July 2020 and evaluated the effects of adding PLEX to standard remission induction therapy on AAV outcomes at 12 months. The meta-analysis from 2011 [3] was updated by the exclusion of one study with inappropriate follow-up (Glockner *et al.* [6]), updating one of the studies (replacing Szpirt *et al.* [7] by Szpirt *et al.* [8]) and by the addition of the results from the PEXIVAS trial [3]. A total of 1060 patients were included and data from 999 patients included in the seven studies that reported on the rates of ESKD at 12 months were used for the meta-analysis risk estimation (2/9 were excluded because there was no report of ESKD at the 12-month time point). The authors concluded that the addition of PLEX to standard remission induction in AAV probably reduced the risk of ESKD at 12 months [RR 0.62 (95% CI 0.39–0.98)]. In the subgroup analyses of patients with SCr ≤5.7 mg/dl versus >5.7 mg/dl, there were no differences in the RRs for ESKD at 12 months [RR 0.70 (95% CI 0.43–1.12) versus 0.83 (95% CI 0.56–1.01); $P = .55$]. In addition, the authors defined the risk for ESKD progression at 12 months as low risk (creatinine ≤200 μmol/L), low–moderate risk (creatinine >200–300 μmol/L), moderate–high risk (creatinine >300–500 μmol/L) and high risk (creatinine >500 μmol/L or requiring dialysis) [5] and the absolute risk reduction (ARR) for each category was estimated based on the RR for ESKD at 12 months of the overall population (seven studies) that received PLEX when compared with controls. The meta-analysis showed that PLEX was associated with an estimated ARR for ESKD at 12 months of 16.0% (range 4.2–23.6) for those at high risk (high certainty of important effects). These findings were interpreted as supportive for the addition of PLEX to standard remission induction in patients with AAV and a high risk of progression to ESKD or requiring dialysis [9].

AAV is a rare disease and kidney survival is a determinant of patient survival [10]. Consequently, the efficacy of PLEX in AAV-GN has been explored in patients with severe kidney disease who are at higher risk of progression to ESKD. However, studying the effect of PLEX has proven to be challenging. The number of studies is small, as such meta-analysis methodologies are viewed as a way of achieving rigorous and coherent input from past research [11]. The clinical trials to be included in a systematic review and meta-analysis are selected based on the question outlined following the Population, Intervention, Comparator, and Outcome criteria, which typically are kept consistent between studies that report outcome occurrences in both interventions [12]. In the Walsh *et al.* [5] meta-analysis, with the objective of capturing all the information possible on the use of PLEX for the treatment of AAV-GN, the authors opted for a broad inclusion criterion: 'randomized controlled trials investigating effects of PLEX in patients with AAV or pauci-immune rapidly progressive glomerulonephritis and at least 12 months' follow-up'. For that reason, data from clinical trials with different inclusion criteria and comparators (e.g. the MEPEX trial, which compared PLEX versus methylprednisolone, as compared with the PEXIVAS trial, which compared PLEX versus no PLEX), from studies with no occurrence of ESKD in one of the arms (e.g. Szpirt [8]) or studies that only reflect a subset of the AAV-GN population (e.g. MEPEX trial, which only included patients with SCr >5.7 mg/dl) were combined and analyzed altogether. It should be noted that this meta-analysis analyzed data gathered over 40 years. During this time there has been tremendous and unprecedented improvement in the clinical care of patients with AAV-GN, which had a significant impact on prognosis [13]. This is especially true over the last 2 decades. In parallel, there has been a refinement in clinical trial design and intensified international collaboration that allowed the conduct of the PEXIVAS trial, the largest clinical trial on AAV ever conducted. It was therefore surprising to find that the results of the meta-analysis did not mirror the results of the PEXIVAS trial, i.e. no benefit of adding PLEX to standard remission induction therapy in

Table 1: Risk of ESKD at 12 months in patients at high risk of progression to ESKD.

Number of studies	Studies	RR[a]	Patients who were not treated with PLEX and evolved to ESKD (control group)[b], %	Patients who received PLEX but evolved to ESKD, %	ARR[c], %	NNT[d], %
7 studies	Rifle 1980 [20] Pusey 1991 [21] Cole 1992 [22] Guillevin 1997 [23] Jayne 2007 (MEPEX) [1] Szpirt 2011 [8] Walsh 2020 (PEXIVAS) [4]	0.58[e]	38	$0.58 \times 0.38 = 22$	$38 - 22 = 16$	$1/16 = 6$
6 studies	Rifle 1980 [20] Pusey 1991 [21] Cole 1992 [22] Guillevin 1997 [23] Jayne 2007 (MEPEX) [1] Szpirt 2011 [8][f] Walsh 2020 (PEXIVAS) [4]	0.68	38[h]	$0.68 \times 0.38 = 25.8$	$38 - 25.8 = 12.2$	$1/12.2 = 8$
5 studies	Rifle 1980 [20] Pusey 1991 [21] Cole 1992 [22] Guillevin 1997 [23] Jayne 2007 (MEPEX) [1][g] Szpirt 2011[8][f] Walsh 2020 (PEXIVAS) [4]	0.83	38[h]	$0.83 \times 0.38 = 31.5$	$38 - 31.5 = 6.5$	$1/6.5 = 15$

[a]RR obtained from Supplementary Tables 1 and 2.
[b]38% is the proportion of patients who did not receive PLEX and evolved to ESKD at 12 months given in Table 3 of Walsh et al. [5]. This proportion was obtained from the control groups population from the seven studies. It is likely that this proportion of patients is lower, particularly when combining only five studies. However, a more accurate calculation is not possible since the authors of PEXIVAS have never presented the data for ESKD at 12 months in isolation.
[c]ARR: the percentage of patients in the control group who did not receive PLEX and evolved to ESKD at 12 months – the percentage of patients who received PLEX and evolved to ESKD at 12 months.
[d]NNT, number needed to treat: 1/ARR.
[e]The authors used the RR corrected for continuity provided in Supplementary Table 2.
[f]Excluded from the analysis because the outcome of ESKD at 12 months was only documented in one arm (control group).
[g]Excluded from the analysis because only patients with SCr >5.7 mg/dl were included in this trial.
[h]Because the number of patients who evolved to ESKD at 12 months was not provided stratified by risk category, we assumed 38% as constant, the same as used for patients with serum creatinine >5.7 mg/dl in the whole cohort, and calculated the ARR using different combinations of studies.

patients with an eGFR <50 ml/min/1.73 m^2 and in patients with SCr >5.6 mg/dl. It is worth mentioning that although the proportion of patients who received PLEX and required hemodialysis in the PEXIVAS study was similar when compared with the MEPEX trial, the actual number was larger (PEXIVAS 140 patients, MEPEX 95 patients), suggesting a role for improvement in the global kidney disease standard of care over the last 20 years in the assessment of the benefit of adding PLEX to remission induction treatment.

The meta-analysis hypothesized that the subgroup of patients with severe AAV-GN is the one most likely to benefit from PLEX. Therefore the authors further explored the meaning of their findings with subgroup analysis and ARR analysis per risk category (high-risk category: SCr >500 μmol/L or SCr >5.7 mg/dl or requiring dialysis). The five studies that included populations in both subgroups (SCr <5.7 mg/dl and >5.7 mg/dl) and occurrence of the outcome of ESKD at 12 months in both interventions were used for this estimation. This subgroup analysis showed no benefit of PLEX in patients with SCr >5.7 mg/dl or ESKD when compared with patients with SCr <5.7 mg/dl [RR 0.83 (95% CI 0.56–1.01) versus 0.70 (95% CI 0.43–1.12); $P = .55$] (Supplementary Table 1 in the meta-analysis by Walsh et al. [5]). The MEPEX study was not included in this analysis because MEPEX only included one of the populations included in the subgroup analysis (i.e. patients with SCr >5.8 mg/dl), nor the Szpirt *et al.* [8] study because the outcome of ESKD at 12 months occurred in only one of the interventions. To estimate the potential difference in event rates between groups (PLEX versus no PLEX), the authors calculated the ARR according to the risk for ESKD progression at 12 months. This analysis included all the AAV-GN population that received PLEX and reported outcomes of ESKD at 12 months, and therefore seven studies were included, adding back the MEPEX [1] and Szpirt *et al.* [8], instead of using only the previous five studies the authors used to conduct the subgroup analysis, and used the RR corrected for continuity [RR 0.58 (95% CI 0.35–0.97)]. The frequency of ESKD at 12 months in patients at high risk or with SCr >5.7 mg/dl in the control population was 38% and in the group of patients who received PLEX was 22% ($0.38 \times 0.58 = 22\%$), resulting in an ARR of 16% (38%–22% = 16%) (Table 1). In this case, the ARR means that only six patients ($1/0.16 = 6.25$) need to be treated to avoid the progression to ESKD at 12 months in one patient. Assuming that the overall risk in the control group of patients with SCr >5.7 mg/dl is the same as that obtained from the whole cohort (38%), which we acknowledge to be unlikely, we can estimate the ARR using the different combination of studies. If only the MEPEX study is added to the five studies included in the subgroup analysis (six studies in total), then the frequency of ESKD at 12 months in patients who received PLEX is $0.38 \times 0.68 = 25.9\%$, resulting in an ARR of 12.1% (Table 1). Alternatively, if the ARR is derived from the five studies [RR 0.83

(95% CI 0.56–1.01)] that were used for the subgroup analysis estimation (Supplementary Table 1 in the meta-analysis by Walsh *et al.* [5]), then the frequency of ESKD at 12 months in patients who received PLEX is 0.38 × 0.83 = 31.5%, resulting in an ARR of 6.5% (Table 1). This means that ∼15 patients (1/0.065 = 15.4) would need to be treated to avoid progression to ESKD in 1 patient. This last estimation better reflects the importance and influence of the PEXIVAS trial and aligns with the subgroup analysis reported and with the current standard of care for patients with AAV. Therefore we argue that the basis of the recommendation for PLEX depends on which studies are included in the calculation.

The adverse effects of PLEX were also explored. The meta-analysis showed an increased risk of severe infection at 12 months in patients treated with PLEX [RR 1.27 (95% CI 1.08–1.49), moderate certainty] and an attributable risk increase of 13.5% (range 1.5–28.0) for those at high risk of progression to ESKD at 12 months (moderate certainty). The trial sequential analysis (Supplementary Figs. 4 and 6 in the meta-analysis by Walsh *et al.* [5]) showed that while the results suggest that the current information is sufficient to accept at least a 20% relative risk reduction in ESKD, the results also suggest that the current information is sufficient to accept at least a 20% relative risk increase in serious infections. Hence the benefit of PLEX on renal outcomes at 12 months seems to be offset by an increased risk of serious infection, a well-recognized risk factor for early mortality in AAV [10]. This is particularly relevant for patients at high risk of progression to ESKD at 12 months, suggesting the need for clinical trials that specifically include patients with eGFR <15 ml/min/1.73 m^2.

Furthermore, the results of the meta-analysis do not take into consideration the impact of kidney biopsy findings such as the severity of crescentic lesions (crescentic class) or the extent of chronic changes (chronicity grade) in renal function recovery, progression to ESKD or death, and contributing to the prediction of which patient will benefit from PLEX [14–17]. A post hoc analysis of dialysis-dependent patients enrolled in the MEPEX trial showed that for patients treated with PLEX, the chance of dying from therapy was higher than the chance of dialysis independence in the case of severe tubular atrophy and <2% of normal glomeruli [18]. Thus the evaluation of the indication of PLEX in AAV-GN based solely on SCr levels is incomplete and other factors should be included when determining which patients may benefit from the addition of PLEX to remission induction treatment.

Finally, the bulk of the analysis was derived from studies using prednisone and cyclophosphamide for induction therapy, which is starting to differ from current practice, as demonstrated by the recent CCX168 (Avacopan) in Patients With ANCA-Associated Vasculitis trial, in which 65% of patients were treated with a combination of prednisone and rituximab [19]. Moreover, the impact of new immunosuppressant adjunctive therapies should also be taken into consideration. The addition of avacopan [19], a C5a complement inhibitor, to standard remission induction therapy produced a rapid decrease in proteinuria, likely reflecting fast control of ongoing inflammatory processes, with a beneficial effect on the progression to ESKD in patients with severe AAV-GN. The potential efficacy of avacopan in renal recovery at 12 months makes consideration for the use of PLEX perhaps superfluous in future clinical practice. We acknowledge that clinical trials are still needed to evaluate this hypothesis.

For the reasons outlined above, we consider that the benefit of PLEX has not been categorically demonstrated by the meta-analysis and is not conclusive of a definitive recommendation for the use of PLEX to treat patients with AAV-GN at high risk of progression to ESKD at the current time. In addition, the meta-analysis showed no evidence whatsoever of a benefit of PLEX in patients at lower risk of progression to ESKD. Herein we also identified the gaps in knowledge that should be the focus of future research and considered when to address the indication of PLEX in AAV-GN. Further studies that include only patients with eGFR <15 ml/min/1.73 m^2 or dialysis at presentation should be designed to clarify these questions, including the role of kidney biopsy findings in the decision-making process of who might benefit from PLEX and the impact of novel treatments (i.e. C5a inhibitors) in avoiding progression to ESKD at 12 months.

DATA AVAILABILITY STATEMENT

The data of this article are available from the corresponding author upon request.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, including in abstract format. The authors have no conflicts of interest to declare.

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