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ORIGINAL ARTICLE

The role of plasma exchange in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis

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Abstract

Background Plasma exchange (PLEX) in addition to standard immunosuppressive treatment in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AVV) remains controversial. The aim of this study is to evaluate the effect of PLEX on AVV outcomes.

Methods Literature search was performed using Medline, Scopus, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov databases, and Google Scholar. The statistical meta-analysis and leave-one-out analysis were conducted using the Review Manager 5.3 and Open Meta-Analyst software, respectively.

Results Ten studies were included in the meta-analysis comprising 1235 patients; 633 received conventional treatment and 602 were treated with PLEX in conjunction with induction therapy. PLEX was not associated with lower rates of either mortality at 3 (RR: 0.79, 95% CI: 0.19–3.25) and 12 months (RR: 0.73, 95% CI: 0.40–1.34) or ESRD at 3 (RR: 0.30, 95% CI: 0.30–2.42) and 12 months (RR: 1.32, 95% CI: 0.53–3.25). Similarly, no differences were captured concerning disease relapses (RR: 0.92, 95% CI: 0.62–1.36), the incidence of infections (RR: 1.05, 95% CI: 0.63–1.76), and severe adverse effects (RR: 1.04, 95% CI: 0.59–1.81). Time-to-event analysis revealed lower incidence of ESRD (HR: 0.71, 95% CI: 0.55–0.92) among patients who received PLEX, while the overall mortality was similar (HR: 0.96, 95% CI: 0.72–1.29) between the two groups.

Conclusion The present meta-analysis does not support the wide use of PLEX for the management of AAV in routine clinical practice. Future well-designed randomized controlled trials focusing on specific disease-related manifestations are necessary to reach firm conclusions about the potential efficacy of PLEX.

Key Points
- *PLEX is not widely recommended for the management of ANCA-associated vasculitis.*
- *PLEX performance may reduce the overall incidence of ESRD in severe ANCA-associated vasculitis.*
- *Well-designed randomized controlled trials focusing on specific disease-related manifestations are necessary to reach firm conclusions about the potential efficacy of PLEX on AAV-related outcome.*

Keywords ANCA · Plasmapheresis · Plasma exchange · Meta-analysis · Vasculitis

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Introduction

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) are systemic vasculitides of small vessels associated with the presence of antineutrophil cytoplasmic antibodies (ANCA) [1]. Together, these two entities are termed ANCA-associated vasculitis (AAV) representing a common cause of rapidly progressive glomerulonephritis (RPGN) [2]. Its pathogenesis is still poorly understood, albeit the pathogenic role of ANCA (anti-proteinase 3 and anti-myeloperoxidase) is supported by animal studies [3, 4] and rare cases of newborns with systemic vasculitis due to vertically transmitted ANCAs [5]. However, owing to the absence of ANCA in some patients and the inconstant relationship between disease course and the levels of circulating ANCA, the pathogenicity of these antibodies remains to be clarified [6].

The conventional management of AAV includes the administration of high dose-glucocorticoids (GCs) and cyclophosphamide (CYC) in remission-induction phase with good response rates [7]. In recent years, rituximab (RTX) has been introduced in the armamentarium of AAV treatment with comparable efficacy [8, 9]. Although the induction therapy leads to disease remission in up to 90% of the cases [10], patients with AAV still suffer from high mortality, increased rates of end-stage renal disease (ESRD), relapses, and serious adverse events due to aggressive immunosuppression [11, 12].

In the view of poor outcomes with conventional therapy and the possible pathogenic role of ANCA, the use of plasma exchange (PLEX; an extracorporeal therapy that removes high molecular weight components, such as ANCA, from blood) in addition to the standard of care has been proposed to improve clinical outcomes [6]. In this context, several randomized controlled trials (RTCs) and retrospective studies have been conducted to evaluate the effect of PLEX on AAV outcomes, while recent European league against rheumatism/European Renal Association—European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations suggest the use of PLEX as add-on therapy in AAV patients with severe diffuse alveolar hemorrhage (DAH) or serum creatine level of ≥ 500 mmol/L [13].

The largest randomized controlled trial in the field (PEXIVAS) [14] was recently published demonstrating PLEX did not reduce the incidence of ESRD or all-cause mortality. Its results and the several limitations were critically reviewed in the literature putting in doubt the elimination of PLEX in the management of AAV [15, 16]. Nonetheless, no firm consensus exists concerning its exact impact on short, long-term outcomes and specific disease-related manifestations (e.g., pulmonary hemorrhage). The aim of the present meta-analysis is to evaluate the effect of PLEX on patients with AVV and clarify its influence on mortality, ESRD, relapses, and severe adverse events.

Materials and methods

Study design

The meta-analysis was designed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. Selection criteria were pre-determined; studies were considered eligible if they evaluated the rates of mortality, ESRD, or disease relapse among patients with AAV treated with PLEX. Study selection was conducted in three consecutive stages. First, the titles or abstracts of electronic articles were screened to assess their potential eligibility. Second, all articles presumed to meet the selection criteria were retrieved as full-texts. Subsequently, all studies (RCTs or observational) that reported any of the outcomes of interest were included. Case reports, conference abstracts, review articles, and animal studies were excluded from the present meta-analysis. Study selection was performed independently by two authors, while any possible discrepancies were resolved by their consensus or discussed with another author.

Literature search and data collection

Literature search was primarily performed using Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinicaltrials.gov databases. Google Scholar (2004-2019) database along with the reference list of the included studies ("snowball" method) was also systematically searched in order to recognize possible eligible papers. The date of the last search was set at 30 April 2020. The search strategy was based on the following algorithm: "(plasmapheresis OR plasma exchange OR apheresis OR plex OR pex) AND (ANCA OR vasculitis OR glomerulonephritis OR pauci-immune OR alveolar hemorrhage OR pulmonary hemorrhage)."

Data extraction

The extracted data from each article were planned to include the following: name of first author, year of publication, country, study design, inclusion and exclusion criteria, type of immunosuppression, treatment plan of the control group, duration of follow-up, patients' number, age, gender, serum creatinine, type of vasculitis, and dialysis requirement. The outcomes of interest were defined to be as follows: mortality, ESRD, relapse, any serious adverse effect, and serious infections.

Quality assessment

The quality of RCTs was evaluated using the Cochrane risk of bias tool [18]. Risk of bias was assessed to be low, unclear, or

high by taking into account the following domains: random sequence generation, blinding, allocation concealment, incomplete outcome, and selective reporting. Moreover, the quality of observational studies was assessed using the Risk Of Bias In Non-randomized Studies (ROBINS-I) assessment tool [19], which judges the potential presence of bias regarding the domains of confounding, selection, classification, deviation from intended intervention, missing data, and measurement and reporting of the outcomes. Risk of bias assessment was performed by two authors, and any potential disagreement was resolved by their consensus.

Statistical analysis

The statistical meta-analysis was conducted using the Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Confidence intervals (CI) were set at 95%. The inconsistency index (I^2) was calculated as a measure of inter-study heterogeneity [20]; values < 50% were considered to indicate low heterogeneity, values at 50–75% moderate heterogeneity, and > 75% critical heterogeneity. A random-effects model was chosen to provide estimates of risk ratio (RR) and 95% CI. Overall mortality and ESRD were treated as time-to-event data, and thus, hazard ratio (HR) was selected as the optimal measure, as it takes into account both the number and the timing of events [21]. In case HR was not available, it was calculated by reconstructing the Kaplan-Meier curve, taking into consideration the minimum and maximum follow-up periods [22]. Publication bias was evaluated by the visual inspection of funnel plots, since the small number of the available studies rendered the interpretation of statistical tests unreliable.

Sensitivity analysis

Leave-one-out analysis was performed to assess the effects of individual studies on the overall outcome. To achieve this, one study was sequentially omitted, and its influence on the statistical significance of the overall result was evaluated. Leave-one-out analysis was conducted using the Open Meta-Analyst software [23].

Results

Study selection

The study selection process is schematically depicted in the PRISMA flowchart (Fig. 1). Three studies [24–26] were excluded after reading the full-text, since one of them represented a letter to the editor [24], one study lacked a control group [25], and another one included patients with positive anti-glomerular basement membrane antibodies [26]. Overall, 10 studies [14, 27–35] were finally included in the analysis, comprising a total of 1235 patients. Among them, 633 received conventional immunosuppressive treatment, while 602 patients were treated with PLEX in conjunction with standard therapy. The methodological characteristics of the included studies (country, design, eligibility criteria, treatment protocol, follow-up period) are described in Table 1. Four studies were RCTs, while 5 studies adopted a retrospective design. The most common conventional treatment protocol consisted of prednisolone and cyclophosphamide administration, while use of azathioprine, cyclosporine, rituximab, and mycophenolate mofetil was also reported. Median follow-up period ranged from 1 to more than 10 years. The most important patients' characteristics (age, gender, serum creatinine, need of dialysis, and type of vasculitis) are presented in Table 2. No significant differences were noted among the compared groups in the majority of studies.

Quality assessment

Evaluation of RCTs revealed no risk of bias concerning the randomization process, although concerns were raised in the blinding of personnel and participants domain, due to the inherent blinding limitations of the investigated intervention. However, lack of blinding was unlikely to alter the outcome assessment (mortality or ESRD). Moreover, the process of allocation concealment was unclear, while a lack of an available trial protocol precluded the safe exclusion of reporting bias in 2 of the included RCTs (Supplementary Fig. 1). The outcomes of quality assessment of observational studies are presented in Table 3. In particular, ROBINS-I tool indicates an overall low to moderate risk of bias, mainly coming from the domain of confounding in studies with differentiations of patients' baseline characteristics. In addition, moderate risk of bias may have arisen from the selection of participants in 2 studies with unclear eligibility criteria, while bias due to classification of interventions was considered as a concern in another 2 studies using complex immunosuppressive protocols.

Outcomes

The results of the meta-analysis are illustrated in Fig. 2. PLEX did not lead to significantly different rates mortality at 3 (RR: 0.79, 95% CI: 0.19 to 3.25, 272 patients) or 12 months (RR: 0.73, 95% CI: 0.40 to 1.34, 427 patients) and ESRD at 3 (RR: 0.30, 95% CI: 0.30 to 2.42, 380 patients) or 12 months (RR: 1.32, 95% CI: 0.53 to 3.25, 489 patients). Similarly, no significant differences were estimated concerning disease relapse (RR: 0.92, 95% CI: 0.62 to 1.36, 483 patients), as well as the incidence of infections (RR: 1.05, 95% CI: 0.63 to 1.76, 498 patients) or serious adverse effects (RR: 1.04, 95% CI: 0.59 to 1.81, 498 patients) (Appendix 1, Figs. S1–7). Time-to-event data analyses revealed no significant difference of overall

Table 1. Study characteristics.

Study name	Location	Study design	Inclusion criteria	Exclusion criteria	Control group	Immunosuppression	Median follow-up
PEXIVAS trial	Multinational	Multi-center RCT	GPA or MPA; ANCA positivity; eGFR < 50 mL/min/1.73 m^2 or alveolar hemorrhage; age ≥ 15 years	Pregnancy, anti-GBM antibodies, linear glomerular immunoglobulin deposition, dialysis for > 21 days before study, prior renal transplant, contraindication to cyclophosphamide, glucocorticoids, or plasma exchange	Conventional treatment + corticosteroids	IV Methylprednisolone → oral prednisolone, cyclophosphamide or rituximab At 3–6 months: azathioprine	2.9 years
MEPEX trial	Europe	Multi-center RCT	GPA or MPA; biopsy-proven pauci-immune GN; sCr > 500 μmol/L; age 18–50 years	Pregnancy, malignancy, hepatitis B or C, HIV, anti-GBM antibodies, other autoimmune disease, alveolar hemorrhage, dialysis for > 2 weeks before study, prior plasma exchange, prior receipt of cyclophosphamide, azathioprine, high-dose steroids	Conventional treatment + IV methylprednisolone	Prednisolone, cyclophosphamide At 6 months: azathioprine	3.95 years
2010; Szpirt	Denmark	RCT	GPA, biopsy-proven pauci-immune GN	Manifestations from ≤ 2 organs, negative c-ANCA, other autoimmune disease	Conventional treatment	Prednisolone, cyclophosphamide At 3 months: cyclosporine	> 5 years
2002; Zauner	Germany	RCT	GPA or MPA; biopsy-proven pauci-immune GN	Type I or II rapidly progressive GN, other autoimmune disease	Conventional treatment	Prednisolone, cyclophosphamide	10.58 years
2003; Frasca	Italy	RC	GPA or MPA; biopsy-proven pauci-immune GN; AKI	No systemic involvement, other autoimmune disease	Conventional treatment	Methylprednisolone, cyclophosphamide	2.92 years
2012; Gregersen	Denmark	RC	GPA or MPA; biopsy-proven pauci-immune GN; eGFR < 60 mL/min/1.73 m^2; age > 18 years	Any contraindication plasma exchange or immunosuppression, other autoimmune disease	Conventional treatment	Prednisolone, cyclophosphamide Maintenance: azathioprine or MMF	1 year
2015; Dhaun	United Kingdom	RC	GPA or MPA; biopsy-proven pauci-immune GN; sCr > 500 μmol/L	Positive anti-GBM antibodies, other autoimmune disease	Conventional treatment	Prednisolone, cyclophosphamide, rituximab, azathioprine, MMF	2.14 years
2015; Solar-Caf-aggi	Mexico	RC	GPA or MPA; ANCA positivity; rapidly progressive GN or alveolar hemorrhage; age 18–75 years	Eosinophilic GPA, hepatitis B or C, HIV, other autoimmune disease, AKI not related to vasculitis	Conventional treatment	Prednisolone, cyclophosphamide, azathioprine, rituximab	4 years
2014; de Joode	Netherlands	RC	GPA or MPA; sCr > 500 μmol/L or alveolar hemorrhage	Other autoimmune disease	Conventional treatment	Prednisolone, cyclophosphamide, azathioprine	10 years

GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RCT, randomized controlled trial; RC, retrospective cohort; GN, glomerulonephritis; sCr, serum creatinine; AKI, acute kidney injury; HIV, human immunodeficiency virus; ANCA, anti-neutrophil cytoplasmic antibodies; MMF, mycophenolate mofetil

Table 2. Patients' characteristics

Study name	Patient no.	Female gender (%)	Median age (years)	Serum creatinine (μmol/L)	GPA (%)	Dialysis requiring (%)
Plasma exchange vs. control						
PEXIVAS trial	352 vs. 352	42.3 vs. 44.9	62.8 vs. 63.5	327 vs. 336	40.6 vs. 40.6	18.8 vs. 21
MEPEX trial	70 vs. 67	41 vs. 36	67 vs. 66	754 vs. 718	25.7 vs. 35.8	32.9 vs. 28.4
2010; Szpirt	16 vs. 16	25 vs. 19	50 vs. 50	263 vs. 250	100 vs. 100	12.5 vs. 25
2002; Zauner	18 vs. 15	33 vs. 27	55 vs. 55.8	385.4	78.8	33.3
2003; Frasca	13 vs. 13	77 vs. 31*	53 vs. 57	921.2 vs. 648.2	70 vs. 54	70 vs. 54
2012; Gregersen	25 vs. 50	76 vs. 56	64 vs. 67	432 vs. 326	64 vs. 50	20 vs. 18
2015; Dhaun	58 vs. 46	53 vs. 43	60 vs. 61	370 vs. 140*	43 vs. 50	34 vs. 2.1*
2015; Solar-Cafaggi	24 vs. 24	50 vs. 58	48.3 vs. 48.3	NR	88 vs. 71	63 vs. 21*
2014; de Joode	26 vs. 50	38 vs. 44	56 vs. 56	192.9 vs. 190.6	77 vs. 62	NR

NR, not reported; GPA, granulomatosis with polyangiitis

* p value < 0.05

mortality (HR: 0.96, 95% CI: 0.72–1.29) between the two groups, although PLEX was significantly associated with a lower overall incidence of ESRD (HR: 0.71, 95% CI: 0.55–0.92) (Fig. 3). Inter-study heterogeneity was assessed to be low to moderate as it ranged from 0 to 71%. Visual inspection of the funnel plots indicated no evident asymmetry, and thus, publication bias was not suspected (Appendix 2, Figs. S8–14).

Leave-one-out analysis demonstrated that no single study exerted significant effect on the outcomes of death and ESRD at 3 and 12 months, disease relapse, and incidence of adverse effects (Appendix 3, Figs. S15–21). However, time-to event analysis of ESRD was mainly driven by the MEPEX trial, as statistical significance was lost after omitting this study (Appendix 4, Table S1).

Discussion

The present meta-analysis aimed to systematically assemble all available RTCs and observational studies in literature in order to evaluate whether PLEX in addition to standard of care in the patients with AAV improves the overall outcomes. In this meta-analysis, nine studies were included comprising 1235 AAV patients; 633 received only the conventional immunosuppression, while the rest (n = 602) were treated with PLEX as add-on therapy [14, 27–35]. The primary endpoint in most studies was the incidence of ESRD and/or mortality.

Approximately 75% of all participants in the present meta-analysis (n = 903) were retrieved from four RCTs. The first RCT [30] in the field (n = 39) showed no additive improvement in both short- and long-term outcomes in the PLEX group while another small RTC [29] consisting of 32 patients indicated that both patient and kidney survival were significantly better among AAV patients treated with PLEX. Until recently, the largest RTC was the MEPEX (n = 137) which showed no benefit on long-term outcomes [28]. However, the current EULAR/ERA-EDTA recommendation concerning the use of PLEX in AAV patients presenting with serum creatine level of ≥ 500 mmol/L [13] was established based on a meta-analysis [36] rather than the MEPEX results.

Recently, the PEXIVAS multicenter RCT was published including 704 patients with severe AAV, and its primary goal was to address the issue of the role of PLEX in such patients. The findings showed no significant effect of PLEX in lowering the incidence of death or ESRD in comparison with usual treatment, without PLEX. While there was a substantial body of experimental and epidemiologic evidence that pointed to a substantial benefit of PLEX, especially in patients with severe disease, the present study showed no significant effects. Methodological bias may have to be incriminated in both past and current studies. Cortazar et al. [15] and Hohenstein et al. [16] critically interpret the findings of the PEXIXAS and discuss the several limitations calling into question the use of PLEX in specific conditions. Specifically, they debate the potential efficacy of PLEX on renal severe AAV, since PEXIVAS included patients with median entry serum Cr at 3.7 mg/dL while biopsy-proven severe kidney was not required as entry criterion.

In total, five studies adopted retrospective design comprising 332 patients with AAV (less than 30% of all participants). The majority of these studies showed slight improvement of renal function at most recent follow-up or decreased rates of ESRD. Importantly, de Joode et al. [34] highlighted the effectiveness of PLEX as rescue therapy in AAV patients with progressive renal disease despite the standard induction treatment. Concerning the overall survival, only one retrospective study [31] demonstrated better survival rates among patients treated with PLEX.

The findings of the present meta-analysis indicate that the use of PLEX does not influence short-term outcome. Specifically, both mortality and ESRD rates within the first

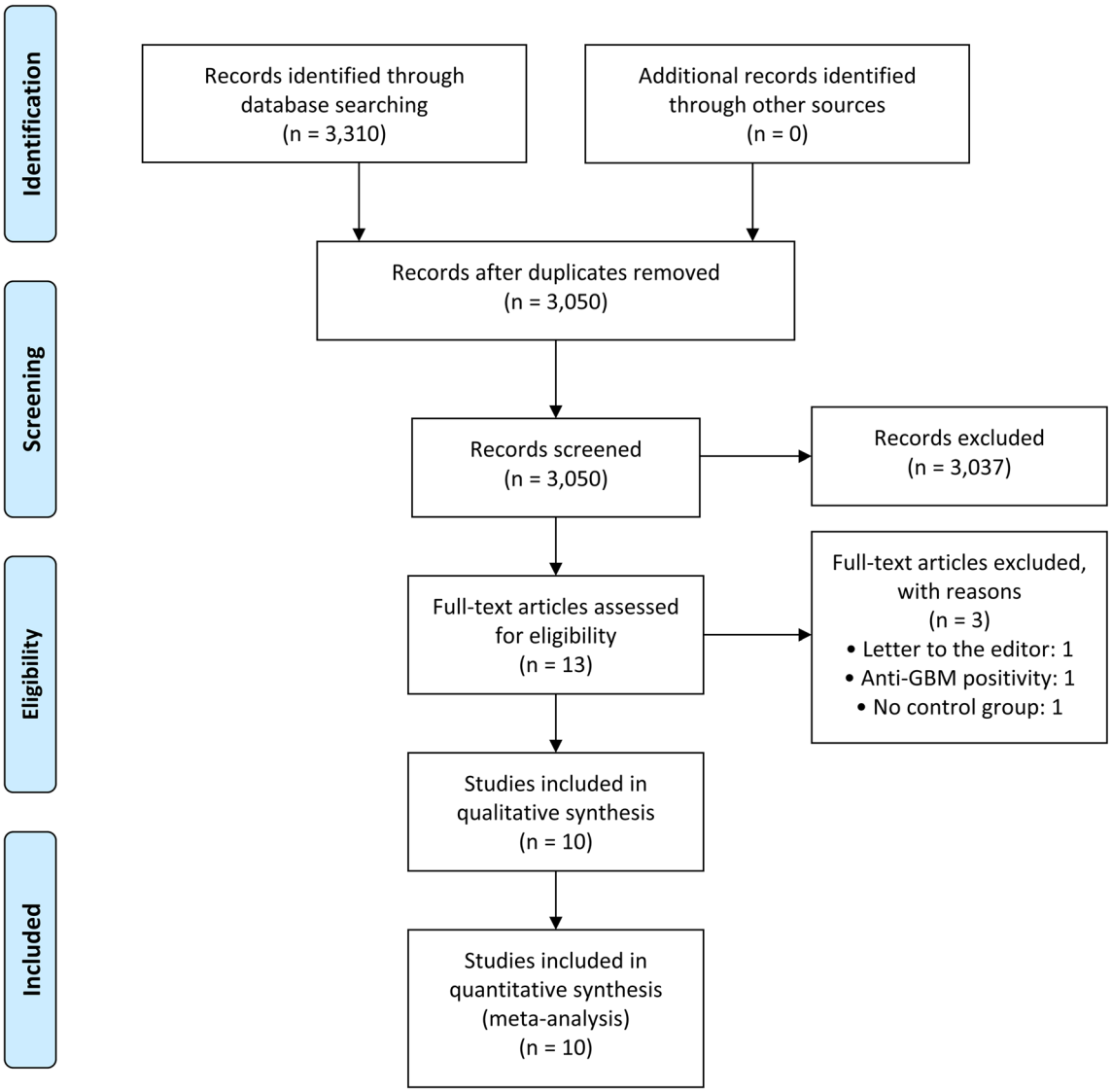

Fig. 1 Search plot diagram

year after diagnosis were similar in both groups. Moreover, the overall mortality remained unaffected. In contrary, the overall incidence of ESRD was significantly reduced among patients receiving PLEX (HR: 0.71). Notwithstanding the protective effect on ESRD, this outcome was mainly affected by the MEPEX trial, since the statistical significance was lost

Table 3 Outcomes of ROBINS-I evaluation

Risk of bias in non-randomized studies—of interventions (ROBINS-I) tool

Year; author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
2003; Frasca	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
2012; Gregersen	Low	Low	Low	Low	Low	Low	Low	Low
2015; Dhaun	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
2015; Solar-Cafaggi	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
2014; de Joode	Low	Moderate	Low	Low	Low	Low	Low	Moderate

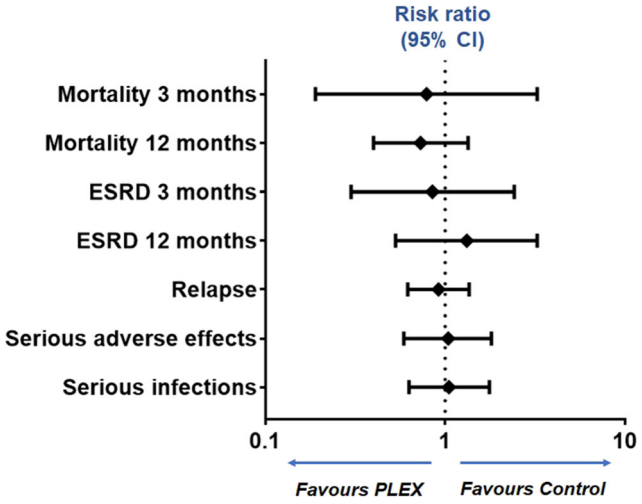

Fig. 2 Forest plots of mortality, end-stage renal disease, relapse, and adverse effects. ESRD, end-stage renal disease; CI, confidence intervals; PLEX, plasma exchange

after excluding this study from the analysis. Also, the effectiveness of PLEX concerning the incidence of ESRD has also been observed in another meta-analysis, which assessed the effectiveness of PLEX in patients with renal vasculitis and idiopathic RPGN [36]. In this study, the overall mortality was not influenced by the use of PLEX, which is in line with our result. However, this study had several limitations and did not include patients exclusively with AAV.

The performance of PLEX has been associated with several adverse events ranging from mild to very severe [37]. Furthermore, repeated PLEX procedures remove immunoglobulins, complement, and immune components, leading possibly to an immunodeficient state increasing the likelihood of infections. However, patients treated with PLEX do not exhibit increased rates of infections [38]. In contrast, serious infectious complications have been previously reported in patients treated with PLEX for RPGN [39]. Our results showed that there are no increased rates of either severe adverse events or infections among patients who received PLEX supporting the safety of this procedure.

Strengths and limitations of the study

Several strong points were evident in the present meta-analysis. To our knowledge, this study represents the first meta-analysis performed evaluating the effects of PLEX on both short- and long-term outcomes in patients with AAV. Ten studies have been included in the final meta-analysis accumulating a large number of patients ($n = 1235$) given the rarity of the disease. This was conducted by thoroughly reviewing 5 independent literature databases without date and/or language restrictions. We focused only on outcomes with clinical significance evaluating both short- and long-term outcomes. Also, time-to event analysis was performed in order to estimate the overall incidence of ESRD and mortality. Importantly, both inter-study heterogeneity and overall risk bias were estimated to be low to moderate.

However, we have to acknowledge a number of limitations. Five out of ten studies adopted a retrospective design. Baseline patients' characteristics were not similar among different studies, although no significant differences were

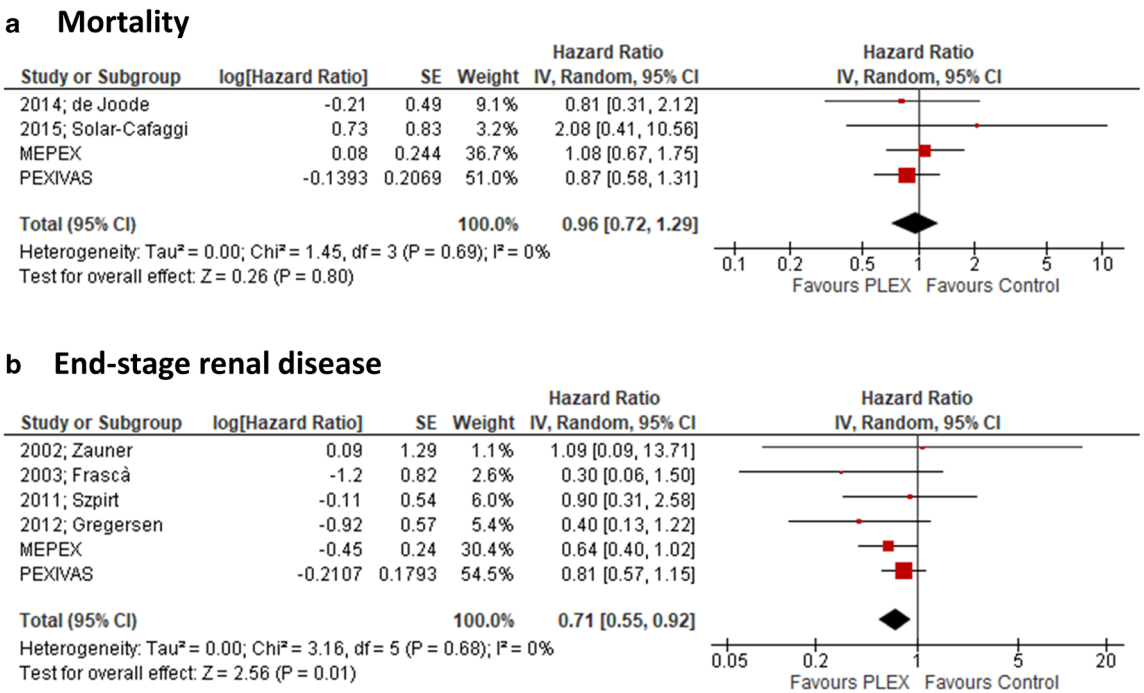

Fig. 3 Forest plot of overall mortality and end-stage renal disease. PLEX, plasma exchange

captured between the 2 groups within the same study. The majority of patients were treated with cyclophosphamide and GCs in induction-remission phase. Nonetheless, some patients were treated with RTX (induction therapy), and all of them received different kinds of treatments in the maintenance phase. Finally, different number of PLEX sessions were performed in each study according to the corresponding protocol.

Implication for current clinical practice and future research

The results of the present meta-analysis call into question the value of PLEX as a routine clinical practice used as add-on therapy, not supporting the use of PLEX in the management of AAV. This statement is mainly supported by the negative effect of PLEX on overall mortality in addition to the negative results of PEXIVAS [14].

Although our analysis showed significantly decreased overall incidence of ESRD, this result was mainly driven by the MEPEX trial. In addition, the MEPEX trail per se did not show any positive effect of PLEX on long-term outcome, including mortality and ESRD [28]. Taking into account this instinct finding and the negative results of PEXIVAS [14], PLEX may not prevent the development of ESRD. Thus, this clinical question may warrant further exploration.

DAH represents a life-threatening complication of AAV which is associated with poor prognosis. The use of PLEX is recommended in patients with severe DAH with low evidence (3C) based on observational studies [13]. Given the rarity and severity of this manifestation, there are only observational studies evaluating the effect of PLEX on DAH due to AAV. Thus, there is a paucity of data regarding this question. Our meta-analysis is not able to address this question since it includes few patients with DAH. To our knowledge, the largest observational study, including 73 patients with DAH secondary to AAV, showed no benefit of the addition of PLEX to standard induction treatment [40]. Given that 27% of AAV patients participating in PEXIVAS had DAH at the time of enrollment, a subgroup analysis will shed light on this clinical question [14].

To this end, several combinations for the induction remission treatment of severe AAV have been proposed to improve clinical outcomes. The current therapeutic options include high dose of GCs, RTX, and CYC and the use of PLEX, while other disease-modifying anti-rheumatic drugs (DMARDs), such as azathioprine and mycophenolic acid, are mainly used for maintenance treatment. Due to several different combinations of these drugs and the rarity of the disease, there is no strong evidence according to the current literature supporting the effectiveness of one combination over to another. Future randomized controlled trials focusing on different therapeutic combinations are warranted to explore which treatment represents the most effective and less toxic clinical approach.

Conclusions

The findings of the present meta-analysis do not support the wide use of PLEX for the management of AAV, since it did not lead to decreased overall mortality rates. Although there are encouraging data indicating a potentially decreased incidence of ESRD in the long-term among patients receiving PLEX, our data in addition to the negative data of PEXIVAS put in doubt the use of PLEX for this purpose. As a result, the exploration of that specific group of patients, who would be better enhanced of PLEX, in refer to the development of severe and end-stage kidney disease is warranted. Future, well-designed randomized controlled trials focusing on hard outcomes are necessary to reach firm conclusions about the potential efficacy of PLEX as a routine clinical practice in severe, specific AAV-related manifestations.

Compliance with ethical standards

Disclosures None.

Research involving human participants and/or animals For this type of study, formal consent is not required.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was not required since no patients participated the study.

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