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Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis

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Disclosures

Michael Walsh has no conflicts of interest to disclose.

Fausta Catapano has no conflicts of interest to disclose.

Wladimir Szpirt has no conflicts of interest to disclose.

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David Jayne has no conflicts of interest to disclose.

Author's Contributions

Michael Walsh contributed to the concept, design, data collection, analysis, interpretation, and manuscript preparation of this study.

Fausta Catapano contributed to the data collection, interpretation and manuscript preparation of this study.

Wladimir Szpirt contributed to the concept, data collection, interpretation, and manuscript preparation of this study.

Kristian Thorlund contributed to the design, analysis, interpretation, and manuscript preparation of this study.

Annette Bruchfeld contributed to the concept, interpretation, and manuscript preparation of this study.

Loic Guillevin contributed to the concept, interpretation, and manuscript preparation of this study.

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Peter Merkel contributed to the concept, interpretation, and manuscript preparation of this study.

Charles Pusey contributed to the concept, interpretation, and manuscript preparation of this study.

Marion Haubitz contributed to the concept, interpretation, and manuscript preparation of this study.

David Jayne contributed to the concept, design, data collection, interpretation, and manuscript preparation of this study.

Ethics Committee Approval

This study dealt with only published aggregate data and was exempt from requiring approval at the local ethics committee.

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Abstract

Background—Plasma exchange may be effective adjunctive treatment for renal vasculitis. We performed a systematic review and meta-analysis of randomized control trials of plasma exchange for renal vasculitis.

Study Design—Systematic review and meta-analysis of manuscripts identified from electronic databases, bibliographies, and studies identified by experts. Data was abstracted in parallel by two reviewers.

Setting & Population—Adults with idiopathic renal vasculitis or rapidly progressive glomerulonephritis

Selection Criteria for Studies—Randomized controlled trials that compared standard care with standard care plus adjuvant plasma exchange in adult patients with either renal vasculitis or idiopathic rapidly progressive glomerulonephritis.

Intervention—Adjuvant plasma exchange

Outcome—Composite of end-stage renal disease or death.

Results—We identified 9 trials including 387 patients. In a fixed-effects model the pooled relative risk of end-stage renal disease or death was 0.80 for patients treated with adjunctive plasma exchange compared to standard care alone (95% confidence interval 0.65 to 0.99; $p=0.04$). No significant heterogeneity was detected ($p=0.5$; $I^2=0\%$). The effect of plasma exchange did not differ significantly across the range of baseline serum creatinine values ($p=0.7$) or number of plasma exchange treatments ($p=0.8$). The relative risk for end-stage renal disease was 0.64 (95% confidence interval 0.47 to 0.88; $p=0.006$) while the relative risk for death alone was 1.01 (95% confidence interval 0.71 to 1.4; $p=0.9$).

Limitations—Although the primary result was statistically significant, there is insufficient statistical information to reliably determine if plasma exchange reduces the composite of end-stage renal disease or death.

Conclusions—Plasma exchange may reduce the composite endpoint of end-stage renal disease or death in renal vasculitis. Further trials are required given the limited data available.

Keywords

vasculitis; glomerulonephritis; plasma exchange; meta-analysis

Introduction

Wegener's granulomatosis and microscopic polyangiitis are autoimmune diseases often associated with the presence of circulating anti-neutrophil cytoplasm antibodies (ANCA) and are a common cause of rapidly progressive glomerulonephritis (RPGN) 1. The majority of cases of RPGN have a pauci-immune pattern on immunofluorescence and have

circulating ANCA, representing a form of ANCA associated vasculitis (AAV). The introduction of immunosuppression and glucocorticoids has improved outcomes 2, 3 but AAV still has high rates of end-stage renal disease (ESRD) and mortality, particularly in those with glomerulonephritis and low kidney function at presentation 4, 5.

Plasma exchange (PLEX) is a method of removing circulating plasma constituents (e.g. immunoglobulins) and may be an effective treatment for inflammatory autoimmune diseases mediated by auto-antibodies 6. PLEX was proposed as a treatment for severe forms of idiopathic RPGN, the majority of which were due to AAV, based on early anecdotal reports 7, 8. The biologic plausibility of PLEX in AAV has been advanced by discovery of circulating ANCA and their putative pathogenic role 9, 10. Given AAV remains complicated by unacceptably high ESRD and death rates, the addition of PLEX to the standard of care has been studied in several clinical trials.

We systematically reviewed available literature for randomized control trials (RCTs) examining the effect of PLEX in idiopathic RPGN and AAV with renal involvement to understand the effect of adding PLEX to standard therapies on the outcomes of ESRD and death.

Methods

Search Strategy

We searched Medline, EMBASE and the Cochrane Controlled Clinical Trials Register (all to August 2009) using the OVID search engine and two comprehensive search themes which we combined with the Boolean operator “and”. The first theme used terms for vasculitis or glomerulonephritis while the second used terms for plasma exchange. The results were filtered for randomized controlled trials 11.

We identified additional citations from reference lists of review articles, conference proceedings of the American Society of Nephrology (2003 to 2008) and through experts.

Study Selection and Data Abstraction

Two individuals (MW and FC) independently evaluated articles for eligibility in a two stages. First, all identified abstracts were reviewed. Those that met the inclusion criteria, or for which there was uncertainty, were selected for full text review in the second stage. In the second stage full text articles were evaluated for inclusion criteria. Inclusion criteria consisted of: 1) study design (RCT); 2) study population (patients with AAV with renal involvement or RPGN of which >75% were reported pauci-immune or idiopathic); and 3) the outcome (trials that report mortality or renal function parameters). Studies were eligible for inclusion whether published in full or abstract form and irrespective of language.

The same reviewers extracted data in duplicate from all eligible studies to a standardized form. Disagreements were resolved by consensus with a third author (DJ). Extracted data included study design, details of the treatment protocol, and baseline demographic, clinical and laboratory data. The methodological quality of the included studies was assessed using the criteria suggested by Jadad et al (i.e. method of randomization, blinding, use of placebo, reporting of losses to follow-up) 12. Additionally, we abstracted data on allocation concealment, intention to treat analysis and comment on important baseline differences between groups.

Study Outcomes

The primary outcome was the composite of ESRD (defined as dialysis dependency or renal transplantation) or death. A composite outcome was chosen to account for the potential of death to act as a competing endpoint for ESRD (i.e. patients that die cannot develop ESRD and a therapy that results in excess death may therefore appear superior in terms of preventing ESRD). Conversely, follow-up censored at the occurrence of ESRD or other renal parameters may result in differential follow-up. A therapy that results in reduced ESRD may therefore underestimate the effects of the therapy on death because of more complete follow-up. We also assessed the number of adverse events.

Quantitative Data Synthesis

We used the Maentel-Haenszel fixed-effects model to estimate the pooled relative risk with 95% confidence intervals for study outcomes using data from all eligible RCTs¹¹. We performed sensitivity analyses using the DerSimonian and Laird random effect model¹³. The presence of heterogeneity across studies was evaluated using the I^2 and Q statistics¹⁴ and we performed meta-regression to test potential explanations of heterogeneity. We tested for the presence of publication bias using funnel plots, Begg's and Egger's tests. All statistical analyses were performed using Stata ver 10 (Statcorp, College Station, TX).

To assess the reliability of the statistical inferences, from the pooled analysis on our primary outcome (ESRD or death), we calculated the optimal information size (i.e. the required meta-analysis sample size) and applied methods adapted from formal interim monitoring boundaries for cumulative meta-analysis¹⁵. For the optimal information size, we assumed a moderate relative risk reduction of 25% as clinically important and a 38% event rate in the control arm (a conservative estimate from recent trials). We allowed for 30% heterogeneity and required 90% power and a maximum 5% false positive rate. If our meta-analysis did not surpass the optimal information size, we adjusted the thresholds for statistical significance using Lan-DeMets monitoring boundaries for the cumulative meta-analysis Z-statistic^{15, 16}. If the Z-statistic did not cross the monitoring boundaries, we added a hypothetical trial that demonstrated a 25% relative risk reduction to the current meta-analysis to determine how much further evidence is required before subsequent meta-analysis results are unlikely to be falsely positive. The hypothetical trial's size was increased until the cumulative Z-statistic crossed the monitoring boundaries.

Results

Identification of Studies

Progress through stages of the systematic review is summarized in Figure 1. A total of 613 unique citations were identified by our search strategy, of which, 579 were excluded on initial screening. Of the 34 studies that underwent further review, 7 met our eligibility criteria¹⁷⁻²³. We found two additional eligible RCTs from abstract screening and contacting experts; one was available in full text²⁴ and one as abstract only with updated details from the author²⁵ but was subsequently published in full²⁶.

Study Characteristics

A total of 387 patients were included in 9 RCTs, of whom 201 were treated with PLEX and 186 were treated without PLEX (Table 1). One study is a patient level meta-analysis of only the patients with glomerulonephritis from two trials conducted at the same centres^{19, 27, 28}. This study presents data as a single large study and is treated as one study in our analysis. The mean age of patients ranged from 41 to 67 years old of whom the majority were male (64 to 79%). Follow-up ranged from 6 to 127 months. Mean baseline serum creatinine measurements ranged from 3.6 to 13.5 mg/dL in the PLEX group and 3.2 to 13.1 mg/dL in

the no PLEX group. The vast majority of patients had either AAV or idiopathic RPGN ($\geq 87.5\%$ in every trial; $>95\%$ of patients overall). Three studies included patients with pulmonary hemorrhage^{17, 22, 25}.

Seven RCTs used a cyclophosphamide based treatment regimen in all patients while one trial included no cyclophosphamide²³ and one study treated only some patients with cyclophosphamide¹⁹. Four trials^{19, 21–23} used intravenous methylprednisolone in both PLEX and no PLEX groups while one study²⁰ used intravenous methylprednisolone only in the no PLEX group. One study utilized adjunctive anticoagulation in both study groups²¹. One study utilized azathioprine in addition to cyclophosphamide¹⁷. PLEX prescriptions varied between trials (Table 2). Two trials specified PLEX by centrifugation, two by filter separation, two allowed either according to local practice, and three did not report modality. PLEX treatments ranged between 4 and 28 over 1 to 8 weeks. Albumin was the most common replacement fluid (6 trials) while fresh frozen plasma was the primary replacement fluid in one trial²² and two trials did not specify replacement fluid. The prescribed volume of replacement was variably calculated as absolute volume, percent of plasma volume or volume per unit body weight (Table 2).

Risk of Bias

Only one RCT included greater than 100 patients²⁰. Trial quality was limited (see Supplementary Table S1 [provided as online supplementary material]). Unsurprisingly given the nature of the intervention, no trials were blinded or utilized placebo/sham procedures. Allocation concealment was not described in any of the trials. There were small but potentially meaningful differences between groups in studies. For example, the proportion of patients on dialysis at randomization in each group differed in the trials by Glockner et al (PLEX group 50% vs control group 27%), Cole et al (PLEX group 25% vs control group 44%), and Guillevin et al (PLEX group 35% vs control group 15%) although these differences were less pronounced over the trials taken as a whole (PLEX groups 44% vs control groups 46%). Baseline serum creatinine levels were similar between PLEX and control groups in all trials except Guillevin et al (PLEX group 5.0 vs control group 3.2 mg/dL) although the stability or rate of change of these values is not clear in any trial.

Quantitative Data Synthesis

All nine trials were included in quantitative analyses. Overall there were 183 events. No individual study showed a significant difference between the PLEX and no PLEX groups with respect to the primary outcome (the composite of ESRD or death). The pooled relative risk of ESRD or death for PLEX treated compared to no PLEX patients was 0.80 (95% CI 0.65 to 0.99; $p=0.04$) (Figure 2). There was minimal between trial heterogeneity (I^2 0.0%; Q statistic p -value 0.45).

Figure 3 presents the analysis of death as an endpoint and demonstrates a RR of 1.0 for PLEX compared to control (95% CI 0.71 to 1.42; $p=0.9$) with minimal heterogeneity between trials ($p=0.4$; $I^2=3.9\%$). Figure 4 presents the analysis of ESRD as an endpoint and demonstrates a RR of 0.64 for PLEX compared to control (95% CI 0.47 to 0.88; $p=0.007$) with minimal heterogeneity ($p=0.5$; $I^2=0\%$).

PLEX had the largest effect in the studies with the lowest baseline serum creatinine (Guillevin and Szpirt). However, meta-regression using mean baseline serum creatinine as the independent variable had no significant association with the primary composite outcome ($p=0.7$), death ($p=0.3$) or ESRD ($p=0.8$). Similarly, the minimum number of PLEX treatments was not associated with the effect of PLEX ($p=0.8$). A sensitivity analysis omitting the study by Jayne and colleagues due to differences in intravenous glucocorticoid

treatment did not significantly alter the point estimate of the effect (RR 0.84 compared to 0.80) although the result was no longer significant ($p=0.2$). Random effects models made little difference in the effect estimates but marginally widened the confidence intervals for each outcome. Using a random effects model, the pooled estimate for the composite endpoint of ESRD or death was 0.82 (95% CI 0.67 to 1.01), for death it was 0.97 (95% CI 0.67 to 1.42) and for ESRD it was 0.67 (95% CI 0.49 to 0.91). Similarly, sensitivity analyses in which cases that were unlikely AAV or studies that contained cases that were definitely not AAV, made no material difference to the estimated effect of PLEX on the composite endpoint of ESRD or death (RR 0.81; 95% CI 0.66 to 1.00). Little data was available on adverse event rates between treatment arms. There were no gross differences in adverse event rates or severe infection rates in the studies that presented data (Table 3).

There was no evidence of publication bias using either Egger's test ($p=0.7$) or Begg's test for asymmetry ($p=0.1$) although there were few trials from which to draw conclusions.

Reliability and Conclusiveness of Results

Although the primary result of this meta-analysis was statistically significant result, the calculated optimal information size suggests at least 1478 patients are required to be confident that PLEX provides at least a 25% relative risk reduction. The monitoring boundaries have not been crossed indicating that the cumulative evidence is unreliable and inconclusive (i.e., there is inadequate information to conclude that PLEX effectively reduces ESRD or death despite the p -value below the conventional limits of significance). We calculated that the addition of a hypothetical trial that randomizes only 500 patients and demonstrates at least a 25% relative risk reduction to the current meta-analysis, would provide sufficient information according to the stopping rules to have confidence that PLEX is of at least moderate benefit in AAV (Figure 5).

Discussion

In this meta-analysis of 9 trials including 387 patients we could not demonstrate that there is conclusive evidence that adjunctive PLEX reduces ESRD and death in patients with AAV. Despite statistically significant results suggesting a 20% relative risk reduction, there are too few patients randomized and sensitivity analyses were not sufficiently robust to reliably conclude that PLEX has at least a moderate reduction of the composite endpoint of ESRD or death. Further, whether PLEX affects survival or only the development of ESRD is unclear.

PLEX has a strong rationale to support its use in AAV. There is evidence that suggests ANCA are pathogenic⁹⁻¹⁰. The rapid removal of ANCA may therefore result in rapid control of disease activity and prevent the accumulation of organ damage. PLEX also removes proinflammatory mediators which would augment the clinical effects of autoantibody clearance⁶. Although previous studies suggested PLEX may only be efficacious in patients with substantially decreased kidney function¹⁷, we observed no significant decrement in the effect of PLEX across a range of serum creatinine at study entry. Furthermore, although there was no significant difference in the effect of PLEX on the composite endpoint across the spectrum of kidney function, there were trends towards benefit in preventing death in trials enrolling patients with more preserved kidney function and benefit in preventing ESRD in trials enrolling patients with lower kidney function. Differences both within and between trials with respect to the timing of PLEX in relation to the onset of disease may also have resulted in differing results. One would expect PLEX to be most useful when instituted early in patients with severe underlying disease (i.e. before the onset of significant renal scarring). However, discriminating between patients with and without significant scarring is difficult and not documented well in the trials in this meta-analysis.

We noted a large apparent effect of PLEX on ESRD but no apparent effect on mortality. One would assume that a reduction in ESRD would result in a decrease in overall mortality. Patients with ESRD due to AAV may, however, have reasonable survival on dialysis or with transplantation and therefore extend their lives beyond the follow-up duration of most studies. Additionally, some studies likely censored follow-up time at the point of ESRD and therefore lost information on differential survival rates. Alternatively, death due to severe infection rather than ESRD or progressive AAV is common in patients with very low kidney function and PLEX would not be expected to have a major impact on this causal pathway, thus the effects of PLEX on death would therefore be diluted or the effects of PLEX on death may be negligible. However, ESRD is associated with poor health related quality of life and high health care costs and the prevention of ESRD alone is an important advance for patients with AAV.

Few patients with pulmonary hemorrhage were included in the trials. This is likely due to a prevalent belief that PLEX is medically indicated for patients with pulmonary hemorrhage on the basis of observational data and the systematic exclusion of these patients from most trials. Although data on patients with lung hemorrhage was insufficient to perform meaningful subgroup analyses, it is notable that none of the three trials that included these patients made special mention of particularly poor outcomes in patients with lung hemorrhage not treated with PLEX. Further, infection is the most commonly cited cause of death in these patients irrespective of whether PLEX was given^{29, 30}. Together, these data call to question the utility of PLEX in patients with pulmonary hemorrhage.

Our meta-analysis has several notable strengths. We utilized objective and clinically important endpoints. This is particularly notable given the difficulty in performing RCTs in rare diseases like AAV. Establishing effective therapies is, however, important given the poor outcomes of patients with AAV. Although several RCTs in AAV have demonstrated the non-inferiority of reduced toxicity regimens compared to standard regimens^{31–35}, there has been little progress in establishing therapies that are more effective than cyclophosphamide and glucocorticoids. It is therefore a major advancement in the field of AAV to demonstrate that PLEX may reduce the occurrence of important clinical endpoints. Furthermore, no other adjuvant treatments or alternate treatment regimens have ever shown trends to improved mortality or ESRD rates in AAV. PLEX therefore represents the best candidate to improve patient-important outcomes in AAV.

Although our meta-analysis is encouraging, it should be interpreted in light of its limitations. The included studies were heterogeneous with respect to the treatment regimens, the patients included and the duration of follow-up. It is reassuring that despite these clinical disparities there was no statistical heterogeneity and results from the random-effect models are similar to the fixed-effect models. Further, sensitivity analyses excluding all patients without confirmed AAV did not demonstrate significant differences from the primary analysis. Also, although our meta-analysis is comprehensive it still does not reach optimal information size. Despite this, PLEX has accumulated more evidence any other therapy in this rare disease and the addition of a trial of 500 patients demonstrating at least a 25% relative risk reduction would reliably confirm a treatment effect of at least moderate size. A trial of this size failing to demonstrate a 25% relative risk reduction would require further trials be undertaken.

We demonstrated that PLEX is a promising therapy and may improve clinically meaningful outcomes in a broad spectrum of patients with AAV. Despite statistically significant results, we also found that according to monitoring boundaries for meta-analyses and the calculated optimal information size, enthusiasm for PLEX in AAV must be tempered. Until further RCT data is available, widespread use of PLEX for patients with renal vasculitis cannot be endorsed due to its expensive, resource intensive and invasive nature. PEXIVAS (ISRCTN

number 07757494/Clinicaltrials.gov number NCT00987389), a trial underway that is powered to detect a moderate to large treatment effect of PLEX may provide sufficient additional information to make confident statements about the efficacy of PLEX for AAV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Literature search and selection.

Figure 2. Forest plot of the effects of adjunctive plasma exchange (PLEX) on the composite endpoint of end-stage renal disease or death in patients with ANCA associated vasculitis.

Figure 3. Forest plot of the effects of adjunctive plasma exchange (PLEX) on the endpoint of death in patients with ANCA associated vasculitis.

Figure 4. Forest plot of the effects of adjunctive plasma exchange (PLEX) on the endpoint of end-stage renal disease in patients with ANCA associated vasculitis.

Figure 5.

Results of a cumulative meta-analysis after the addition of a hypothetical trial, including 500 patients and demonstrating a 25% relative risk reduction, to the current meta-analysis results. The intersection of the Moderate Evidence and Cumulative Z-statistic lines demonstrates the number of patients required to achieve moderate evidence for the effect of PLEX.

Table 1

Characteristics of patients included in trials for meta-analysis.

Study	Follow-Up (months)	N		Age (mean years)		Female (%)		Baseline Creatinine (mg/dL)		Dialysis at Entry (%)		Lung Hem
		PLEX	Ctr	PLEX	Ctr	PLEX	Ctr	PLEX	Ctr	PLEX	Ctr	
Rifle (1980)	22	6	8	41	52	50	25	10.1	12.9	67	88	No
Mauri (1985)	NR	12	10	NR	NR	NR	NR	13.5	13.1	50	50	NR
Glockner (1988)	6	16	15	56	47	38	20	6.6	6.8	50	27	NR
Pusey (1991)	58	25	23	52	51	36	39	9.0	7.2	44	34	Yes
Cole (1992)	12	16	16	NR	NR	NR	NR	7.2	9.0	25	43	NR
Guillevin (1997)	12	19	13	47	62	47	38	5.0	3.2	32	15	NR
Szpirt (1999)	60	16	16	58	56	25	19	3.6	3.8	13	25	Yes
Zauner (2002)	127	21	18	55	56	29	22	NR	NR	NR	NR	Yes
Jayne (2007)	12	70	67	67	66	41	36	8.5	8.1	67	71	No

PLEX=plasma exchange group; Ctr=control group; Lung Hem=patients with lung hemorrhage included; NR = not reported NOTE: multiple serum creatinine by 88.4 to obtain values in $\mu\text{mol/L}$

Table 2

Characteristics of treatments in trials for meta-analysis.

Study	PLEX Method	Number of PLEX	Volume/ PLEX	Weeks of PLEX	CYC	IV MeP
Rifle (1980)	NR	Up to 28	1.5 plasma volumes	Up to 8	Yes	Yes
Mauri (1985)	Either	6	3.5 L	2	Yes	No
Glockner (1988)	Filter	≥9	50 ml/kg	4	Yes	No
Pusey (1991)	Centrifuge	9	4 L	1 to 5	Yes	No
Cole (1992)	Centrifuge	≥10	1 plasma volume	2,25	No	Yes
Guillevin (1997)	Either	9 to 12	60 ml/kg	3	Some	Yes
Szpirt (1999)	Filter	6 to 12	4 L	2	Yes	No
Zauner (2002)	NR	3 to 12	40 ml/kg	NR	Yes	Yes
Jayne (2007)	Either	7	60 ml/kg	2	Yes	Non-PLEX Only

PLEX=plasma exchange; CYC=cyclophosphamide; IV MeP=intravenous methylprednisolone; NR = not reported

Table 3

Summary of adverse events reported.

Study	Adverse Events n/N (%)		Infections n/N (%)	
	PLEX	Ctr	PLEX	Ctr
Rifle (1980)	1/6 (17)	0/8 (0)	1/6 (17)	0/8 (0)
Mauri (1985)	NR	NR	NR	NR
Glockner (1988)	5/16 (31)	5/15 (33)	4/16 (25)	4/15 (27)
Pusey (1991)	NR	NR	5/25	3/23
Cole (1992)	NR	NR	4/16 (25)	2/16 (13)
Guillevin (1997)	NR	NR	NR	NR
Szpiert (1999)	2/16 (13)	2/16 (13)	2/16 (13)	1/16 (6)
Zauner (2002)	NR	NR	NR	NR
Jayne (2007)	35/70 (50)	32/67 (48)	31/70 (44)	30/67 (45)

NR = not reported