Plasma exchange in antineutrophil cytoplasmic antibody-associated vasculitis—a 25-year perspective

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ABSTRACT

Demonstration of a pathogenic role for antineutrophil cytoplasmic antibodies (ANCA) underlies the scientific rationale for plasma exchange (PLEX) in the treatment of ANCA-associated vasculitis (AAV). Most clinical evidence of efficacy concerns the use of PLEX for the recovery of renal function in severe nephritis, when used in conjunction with immunosuppressive drug therapy. The development of PLEX for this indication, the strength of the clinical trial evidence supporting its use, its roles in other AAV indications and ongoing research are discussed.

Keywords: ANCA, autoantibody, clinical trial, kidney, plasma exchange, vasculitis

INTRODUCTION

The use of plasma exchange (PLEX) in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is still controversial [1]. The accepted indications for use are severe renal disease and pulmonary haemorrhage, as described in the KDIGO guidelines (seven treatments over 14 days, 60 mL/kg replaced with 5% albumin) [2]. However, the controversy refers to the definition of renal severity. The rationale for PLEX is the removal of ANCA-antibodies and other circulating factors involved in the pathology of AAV. Furthermore, 5–10% of AAV patients are ANCA-negative, so the removal of other plasma constituents such as cytokines, complement components and neutrophil microparticles may be therapeutically beneficial as well [3, 4]. Although it has been 34 years since ANCA antibodies were described and later proved to be pathogenic in a murine vasculitis MPO-ANCA model, randomized controlled trials (RCT) which support more extensive addition of PLEX to immunosuppressive induction therapy are still lacking. There are no data on how many AAV patients receive PLEX and as of 2012, only 3–4% of all PLEX treatments are prescribed in AAV patients [5]. The use of PLEX appears to vary among different centres and countries as reported in the PEXIVASC survey (coordinator W. Szpirt) in 2004 which was distributed among EUVAS members [6]. Thirty-three centres answered and they represented up to 320 patients annually (Table 1).

Eight centres included negative ANCA binding levels in their decision of when to stop, six centres took no notice of ANCA levels while others looked for renal recovery and clinical evaluation to guide PLEX dosing. Concerning immunosuppression administered in conjunction with PLEX, 21 (64%) centres performed methylprednisolone (MP) pulses, mostly three times 1 g daily, a few 0.5 g per day, 1 centre gave 1 g monthly, 16 (48%) centres used cyclophosphamide (CYC) pulses, majority six to eight times. Orally (52%) 2.5 mg/kg CYC was given, two centres went for 1.5 or 2.5 mg/kg. Prednisolone (Pred) was given in the majority of centres as 1 mg/kg (88%), three centres started lower, 0.5–0.75 mg/kg, one induced with 30 mg.

PLEX IN GLOMERULONEPHRITIS IN THE PAST

In 1977, Lockwood et al. [7] published the first report describing the use of PLEX in nine patients with crescentic glomerulonephritis (GN), in which five rapidly recovered renal function. This success led to the use of PLEX in the treatment of crescentic GN without anti-GBM antibodies, several years before the discovery of ANCA in pauci-immune GN in 1982. PLEX was subsequently used and reported in...
A surprising observation of the longer term report was a trend towards a reduced relapse risk in the PLEX treatment group (14.4% versus 20.5%, P = 0.14), but this requires confirmation. The relatively small sample size, high mortality and lack of effect on the composite end point have limited the previous expectations that MEPEX could be a ‘game changer’ [1] in PLEX eligibility for AAV.

PLEX is still not commonly performed for AAV, if the serum creatinine is <500 μmol/L. Only one RCT using 32 granulomatosis with polyangiitis (GPA) patients [13] with moderate renal impairment was reported in 2011; it found better preservation of renal function in the PLEX-treated patients with creatinine above 250 μmol/L at 1 month, 3 months, 12 months and 5 years with no effect on mortality or vasculitis relapse rate. Another Danish retrospective study showed that PLEX significantly improved mortality/ESRD/relapses at 12 months in 9 MPO- but not 16 PR3-ANCA positive patients with e-GFR < 60 ml/min compared with historical controls [14].

Two meta-analyses on PLEX in AAV have been published. In 2009, Walsh et al. presented results based on nine RCTs comprising 387 AAV patients [15] and found a reduction in dialysis dependency associated with PLEX (relative risk [RR]: 0.64; 95% confidence interval [CI]: 0.47–0.88), but no reduction in mortality (RR: 1.01; 95% CI: 0.71–1.43) at 12 months was observed. Another meta-analysis reported by Walters et al. [16] found a similar PLEX influence on renal function.

Short-term AAV patient survival is affected by treatment complications, mostly infections and not active vasculitis [17]. Can PLEX be helpful in reducing immunosuppressive total exposure? The sparing effect of PLEX on oral CYC dose has been reported by Szpirt et al. [18], where in a cohort of 132 patients followed for a mean 5.7 years—a low daily CYC dose of 1.5 mg/kg was given to younger patients <65 years and 1.0 mg/kg was given to patients >65 years, compared with the 2.5/2.0 mg/kg/day employed in the MEPEX study. The mortality during this lower oral CYC induction treatment was <5%. In Denmark, a relative mortality in 2005–2013 of 26% (13–52) in GPA was found compared with 100% mortality in 1990–1994 (P = 0.05) that can be attributed to more common PLEX use and lower CYC dose [19].

Recently, a retrospective British multicentre study of 41 dialysis-dependent patients with a severe AAV-GN, where PLEX was combined with Pred and lower i.v. CYC exposure [20], showed similarly a lower mortality of 10% during induction; renal survival was not worse than with a more aggressive CYC regimen.

PLEX for AAV patients with both ANCA and anti-GBM disease has been a standard therapy, and a PLEX schedule similar to anti-GBM disease has been accepted. The outcome of renal survival is similar to anti-GBM nephritis patients but lower when compared with AAV patients without GBM-antibodies [21].

### Table 1. Pexivasc survey

<table>
<thead>
<tr>
<th>Indications</th>
<th>PLEX use</th>
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<tbody>
<tr>
<td>Alveolar haemorrhage</td>
<td>26/33 (79%)</td>
</tr>
<tr>
<td>Creatinine &gt;500 μmol/L</td>
<td>20/33 (61%)</td>
</tr>
<tr>
<td>Creatinine 150–500 μmol/L</td>
<td>5/33 (15%)</td>
</tr>
<tr>
<td>Rapidly progressive GN (RPGN)</td>
<td>7/33 (21%)</td>
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<tr>
<td>Method of PLEX</td>
<td></td>
</tr>
<tr>
<td>Filtration</td>
<td>16/33 (48%)</td>
</tr>
<tr>
<td>Centrifugation</td>
<td>13/33 (39%)</td>
</tr>
<tr>
<td>Either</td>
<td>4/33 (12%)</td>
</tr>
<tr>
<td>Number of PLEX</td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>6/33 (18%)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>17/33 (52%)</td>
</tr>
<tr>
<td>Guided by ANCA</td>
<td>11/33 (33%)</td>
</tr>
<tr>
<td>Guided by clinical response</td>
<td>17/33 (52%)</td>
</tr>
<tr>
<td>Dose of PLEX</td>
<td></td>
</tr>
<tr>
<td>Fixed volume</td>
<td>27/33 (82%)</td>
</tr>
<tr>
<td>According to weight</td>
<td>6/33 (18%)</td>
</tr>
<tr>
<td>Replacement fluid</td>
<td></td>
</tr>
<tr>
<td>Albumin (for low bleeding risk)</td>
<td>21/33 (64%)</td>
</tr>
<tr>
<td>Plasma (for high bleeding risk)</td>
<td>14/33 (42%)</td>
</tr>
</tbody>
</table>

Several nonrandomized studies and case reports in the 1980s and 1990s with both positive and negative results.

### CLINICAL TRIALS OF PLEX IN RENAL VASCULITIS

In 1991, Pusey et al. [8] published a randomized control trial (RCT) that showed a beneficial effect of PLEX in 18 dialysis-dependent patients out of 48, while no outcome difference was found in patients with milder renal deterioration. There was a noticeably high mortality in both PLEX and non-PLEX groups in this study. However, it was then recommended ‘that the routine addition of plasma exchange is unnecessary for patients with milder renal disease (serum creatinine <500 μmol/L), but when renal function is impaired to the point that dialysis is required, the addition of plasma exchange increases the chance of renal recovery’ [9]. This statement on PLEX efficacy in AAV was opposite to the anti-GBM GN PLEX recommendations, which state that dialysis dependency is a bad prognostic factor for PLEX usage and that PLEX is most likely to benefit those with creatinine <500 μmol/L [10].

In 2007, the largest PLEX RCT MEPEX (MEthyl Prednisolone versus Plasma EXchange in vasculitis) study was published [11]. A total of 137 patients with newly diagnosed AAV presenting with creatinine above 500 μmol/L (5.8 mg/dL) or requiring dialysis were randomly assigned to receive seven PLEX sessions and compared with a control group of patients who received three MP pulses of 1000 mg—a common induction treatment in rapidly progressive GN, together with a standard oral CYC of 2.5 and 2.0 mg/kg/day for patients <60 years and Pred of 1 mg/kg/day. At 3 months there was a 24% reduction in dialysis dependency in the PLEX group versus MP controls. At 12 months renal recovery occurred in 69% of the PLEX group and 49% of the MP group with no PLEX impact on mortality (at 1 year 73% versus 76%). The study was criticized for its high mortality rate of 26% at 3 months, mostly due to infections, with no mortality difference between the groups. In 2011, long-term data [12] from MEPEX found that the benefit of PLEX on a reduced ESRD risk was maintained beyond 5 years, but that there was no effect of PLEX on either mortality or the composite of mortality and ESRD.
PLEX FOR NON-RENAL AAV MANIFESTATIONS

The introduction of PLEX in AAV patients with pulmonary haemorrhage is based on a small uncontrolled retrospective study by Klemmer et al. [22]. They reported resolution of pulmonary symptoms in all 20 patients who received PLEX, and 19 survived the initial disease episode. Thirty percent of the patients did not have renal involvement, and 55% were not on mechanical ventilation in these series. Survival for patients with severe alveolar haemorrhage appears to be improving and it is unclear to what extent PLEX is contributing to the improvement [23]. Furthermore, there have been concerns that PLEX could exacerbate haemorrhage by removal of coagulation factors. Replacement of coagulation factors is recommended as a component of the plasma substitution fluid when PLEX is used in patients with active haemorrhage [24]. The PEXIVAS trial (ISRCTN07757494; clinicaltrials.gov NCT00987389) is recruiting patients with alveolar haemorrhage, with or without impaired renal function, and will provide the first randomized controlled trial evidence for PLEX in this life-threatening AAV disease manifestation [25].

Some clinicians also use PLEX for the rare life-threatening neurological or gastrointestinal manifestations of AAV, although there is no consistent evidence of benefit [26]. The Dutch group [27] used PLEX as a rescue therapy (range 5–41 days) in AAV patients, who despite standard induction immunosuppressive therapy showed deterioration of renal function. PLEX patients showed improvement in renal function. They had however a similar long-term outcome concerning both renal and patient survival as matched disease controls. Finally, as mentioned before a retrospective Danish study concluded that PLEX was of value in PR3-ANCA-positive patients, but not in patients, who are MPO-ANCA positive [14]. This tendency, however, was not confirmed by another prospective observational report from Denmark, which did not find the difference in renal outcome between the ANCA subclasses [18].

PLEX COMPLICATIONS

Registry studies have not shown an infection risk, and most complications relate to line insertion, but there is a theoretical risk of hypogammaglobulinaemia, especially if combined with rituximab but there is no guidance on the use of IV Ig. Furthermore vitamin D levels are suppressed [28].

FUTURE DIRECTIONS FOR PLEX IN AAV

At the 15th ANCA workshop in Heidelberg in 2005, a discussion on a launch of a new RCT on PLEX in AAV was initiated based on the previously mentioned Pexivasc survey [6] that was distributed in 2004, which showed that 26 European EUVAS centres were willing to participate in a new RCT, this time eligible to AAV patients with moderate renal disease. Ten centres recommended renal vasculitis with any creatinine (GFR rapidly declining), seventeen centres in patients with creatinine >150, six centres still proposed creatinine >500 and HD dependency.

In 2007 a PEXIVAS protocol meeting was held in Cambridge at which a new PLEX survey [6] (Coordinator M. Walsh) was discussed; the investigators agreed on the inclusion of patients with creatinine above 150 μmol/L and/or pulmonary haemorrhage in a new RCT — PEXIVAS [25] — a 2 × 2 study where PLEX (seven sessions within 2 weeks) and no PLEX control groups are additionally randomized to standard versus low Pred treatment together with oral or i.v. CYC/rituximab for initiation of remission. After funding was secured, the first patient was recruited in June 2010. While preparing the trial, the sample size calculations based on previous clinical trial data found that 500 patients were required to demonstrate a benefit of PLEX on the composite of death and ESRD. Recent registry surveys [29] have indicated improved outcomes for AAV patients with severe renal disease raising the possibility that PEXIVAS might be underpowered. Hopefully, PEXIVAS will help to guide best practice in vasculitis management worldwide, in view of its size and collaborative international nature.

Until the therapeutic mechanism of PLEX is better understood, non-specific plasma removal seems preferable despite the need for plasma product replacement which limits it use where these are in short supply (China). An alternative method of antibody removal, immunoabsorption, has been tested in small numbers of AAV patients and in anti-GBM disease and lupus nephritis [30].

CONCLUSION

Non-randomized, controlled studies and other case series have indicated a renal recovery rate of 75% in PLEX-treated AAV patients, when presenting with renal failure and creatinine >500 μmol/L (5.8 mg/dL). These results appear superior to

Table 2. PLEX procedure recommendations in AAV

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Volume</td>
<td>60 mL/kg replacement with Ringer lactate in 5% albumin as a substitution fluid.</td>
</tr>
<tr>
<td>2. Frequency</td>
<td>If kidney biopsied add two portions of fresh frozen plasma (FFP) on the same day</td>
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<tr>
<td>3. Pulmonary haemorrhage</td>
<td>Seven treatments over 14 days, if possible daily the first 2–3 days</td>
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<tr>
<td>4. AAV in patients with both ANCA- and anti-GBM antibodies</td>
<td>Daily sessions until the bleeding stops and combine with aggressive ultrafiltration if the patient is dialysis dependent and overloaded, then every second day totally up to 10 sessions with FFP as a substitution fluid</td>
</tr>
<tr>
<td></td>
<td>Daily for 14 days or until anti-GBM antibodies are negative or low but above normal limits</td>
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</table>
those reported in a series not using PLEX, where renal function recovery rates of 40–50% have been observed [26]. The PLEX effect on milder renal disease in AAV is still not sufficiently investigated. PLEX appears to be of potential importance in moderation and sparing of immune-suppressive induction regimen in AAV.

The dosing of PLEX and other aspects of the PLEX procedure have been agreed on by consensus but have not been subjected to rigorous clinical investigation; similarly the use of biomarkers, such as ANCA levels, have not been explored to monitor PLEX dosing, in the way that anti-GBM antibody levels are used in anti-GBM disease [23–25]. The removal of plasma proteins complicates the use of biologic therapies, and rituximab is now licensed for the treatment of AAV. Improved understanding of the key effects of PLEX in AAV may indicate other therapeutic targets (Table 2).

**CONFLICT OF INTEREST STATEMENT**

The results presented in this article have not been published previously in whole or part.

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