

Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated Vasculitis (AAV)?

CON

Richard J. Glassock

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Introduction

Vasculitis associated with the formation of ANCA manifests in several forms defined by the extent of organ involvement (renal limited or systemic), with or without granulomatous tissue involvement, and by the presence and nature of the ANCA (antimyeloperoxidase or antiproteinase 3 and associated autoantibodies, in particular antiglomerular basement membrane [anti-GBM] autoantibodies) (1). Severe kidney disease with extensive crescentic involvement and a clinical syndrome of rapidly progressive GN is common in all forms of ANCA-associated vasculitis (AAV) (1). Diffuse alveolar hemorrhage (DAH), of varying severity, can be seen in many kinds of GN (Goodpasture syndrome) but is particularly common in AAV, with or without anti-GBM antibody (2).

The therapy of AAV has greatly improved in recent years, and the use of rituximab (RTX), cyclophosphamide (CYC), or combinations of RTX and CYC plus moderate doses of steroids can effectively and safely induce a complete or partial remission in the great majority of patients (3–5). The role of adjunctive therapy with plasmapheresis (PLEX) has been controversial, except in cases where anti-GBM autoantibody disease is found alone or concomitantly with AAV. The publication of the large Plasma Exchange and glucocorticoid dosing in treatment of anti-neutrophil cytoplasmic antibody associated vasculitis (PEXIVAS) trial in 2020 has generated much attention to this controversy (6).

This debate focuses on this controversy by laying out a precise question: should PLEX be used for severe AKI and/or pulmonary hemorrhage in patients with AAV? For this debate, I will interpret “severe” as meaning the need for artificial organ support (dialysis for AKI or mechanical ventilation for DAH). I will also interpret ANCA vasculitis as meaning a positive (antimyeloperoxidase or antiproteinase 3 autoantibody in the absence of anti-GBM antibody and clinical or morphologic evidence of a vasculitis involving the kidney without or with extrarenal involvement, including DAH. Anti-GBM disease with or without ANCA is generally regarded as an indication for PLEX, and this will not be discussed further. A nuanced answer to this question will likely be neither an absolute yes nor no,

but “it depends.” I will address the severe AKI and the DAH questions separately, although this is an arbitrary dichotomy as patients can and do present with both simultaneously.

PLEX for Severe AKI (Also Known as Rapidly Progressive GN)

Prior to the PEXIVAS trial, a randomized trial of PLEX (in addition to standard immunosuppressive therapy) in severe ANCA vasculitis (serum creatinine level over 5.7 mg/dl or requiring dialysis) showed encouraging results favoring PLEX over the short term. However, the benefits were not sustained over longer-term follow-up (7). A nonstatistically significant trend toward some protection from kidney failure with PLEX was observed (hazard ratio [HR] of 0.64 for kidney failure; 95% confidence interval [95% CI], 0.40 to 1.05). No benefits on all-cause mortality were observed. A larger trial with longer follow-up was clearly needed. Thus, the PEXIVAS trial was conceived and initiated in 2010, and patients were followed for up to 7 years. A total of 704 patients with severe ANCA vasculitis were randomized equally to a regimen of PLEX or no PLEX (seven exchanges over 14 days by centrifugation or membrane separation using 3%–5% albumin as the replacement solution). The frequency or dosing of PLEX was not adjusted to the level of ANCA at randomization. Anti-GBM antibody was an exclusion, and a kidney biopsy was not required for enrollment. The primary composite outcome was death from any cause or ESKD. The trial was event driven, with an 80% power to detect an HR of PLEX of 0.64 at an α of 0.05.

About 29% ($n=205$) of the randomized subjects had a serum creatinine level of ≥ 5.7 mg/dl or were undergoing dialysis, and of these, 68% ($n=140$) were undergoing dialysis. Severe DAH was concomitantly present in about 9% of the subjects ($n=61$). After 7 years of follow-up, the HR for the primary end point was 0.86 (95% CI, 0.65 to 1.17). The HR for kidney failure was 0.81 (95% CI, 0.57 to 1.13). In a subset of patients with a serum creatinine of ≥ 5.7 mg/dl or requiring dialysis, the HR for the primary end point was 0.77 (95% CI, 0.53 to 1.11). Thus, the trial was unable to demonstrate a long-term benefit of PLEX even among

Department of Medicine, Geffen School of Medicine at University of California, Los Angeles, California

Correspondence: Richard J. Glassock, Geffen School of Medicine at the University of California, Los Angeles, 8 Bethany, Laguna Niguel, CA 92677. Email: rjglassock@gmail.com

patients with very severe ANCA vasculitis. ANCA subtype or the medications (RTX or CYC) used to induce remissions made no difference. Interestingly, there was a trend for a more favorable effect of PLEX in patients ≥ 60 years of age in a secondary analysis (HR, 0.75; 95% CI, 0.54 to 1.04) and a harmful effect in those < 60 years of age (HR, 1.20; 95% CI, 0.73 to 1.97).

Although the overall study was well powered to detect an effect of clinical importance, the secondary analyses are subject to a type 2 error and are only hypothesis generating. It should be noted that the intensity of PLEX was not adjusted for ANCA level and that daily PLEX was not required, and we do not have kidney biopsy results to be sure that the degrees of acute and chronic changes were equal in the PLEX and non-PLEX groups. The latter seems highly unlikely because this is a large, randomized study. I would have to conclude, as did the authors of PEXIVAS, that adjunctive PLEX is of no therapeutic value in ANCA vasculitis, either severe or nonsevere in nature, considering its effect on survival or development of dialysis-dependent kidney failure. This means that conventional therapy with RTX and/or CYC plus steroids (in a reduced dosing schedule found to be safe and effective in the PEXIVAS trial; not discussed here) is sufficient for the great majority of patients with severe ANCA vasculitis. Whether a more intensive PLEX regimen (daily PLEX) or one adjusted to ANCA level would show better results is unknown and requires further study. The suggestion that PLEX might be more effective in the very elderly is intriguing, but those data are insufficient to generate any guidelines.

PLEX for Severe DAH

There have been no randomized clinical trials (RCTs) of PLEX for therapy of DAH in ANCA vasculitis; so, we must rely on the weaker evidence provided by observational studies or in secondary analysis of trials, such as PEXIVAS, that included subjects with DAH of varying severity. As with kidney disease, PLEX is always indicated in anti-GBM disease, with or without concomitant ANCA—so, I will confine my remarks to PLEX in ANCA vasculitis without concomitant anti-GBM antibody. The PEXIVAS trial, mentioned above, randomized 61 patients with severe DAH, and the HR for the primary end point (death or kidney failure) was not different between the PLEX and non-PLEX groups (HR, 0.67; 95% CI, 0.28 to 1.64). However, this difference is subject to a type 2 error due to insufficient numbers and the lack of a pulmonary-based end point in the trial (*e.g.*, complete resolution of hemorrhage and successful discontinuance of artificial ventilation). One would have to conclude that PEXIVAS is not very informative of the utility of PLEX in DAH accompanying ANCA vasculitis. Observational studies have also shown variable effects of PLEX for DAH in ANCA vasculitis. The highly influential study of Klemmer *et al.* (8) in 2003 is frequently quoted. In this uncontrolled, retrospective study, 20 of 20 patients had resolution of DAH with intensive PLEX (daily until improvement and then every other day until pulmonary hemorrhage resolved). However, 30% of the patients in this study had normal renal function, and only nine required ventilator support. Those who required dialysis remained dialysis dependent. The number of PLEX sessions averaged

6.2 per patient. All patients were treated with high-dose steroids, and all but two received intravenous CYC. Because of its observational design, conclusions about efficacy of adjunctive PLEX cannot be made with any reasonable degree of certainty. The experience of others with PLEX for DAH in ANCA vasculitis has been much less impressive. For example, Cartin-Ceba *et al.* (9) reviewed a large cohort constituting the Mayo Clinic experience from 1997 to 2012 involving 73 patients with DAH and ANCA vasculitis, 34 of whom were in respiratory failure. Forty-one subjects received PLEX, and 32 did not. Those who received PLEX (in addition to standard therapy for vasculitis) had higher frequency of mechanical ventilation, British Vasculitis Activity Score (BVAS), and active kidney disease. No benefits of PLEX were observed for hospital mortality, duration of mechanical ventilation, or remission. In a literature review of 334 patients from 11 studies, including their own, they found that resolution of DAH and survival to discharge were present in 69 patients treated with PLEX and in 51 not treated with PLEX among 120 patients with sufficient data to estimate outcomes. Taken together, the data do not support an impressive benefit for PLEX, although a positive influence of PLEX in a subset of patients with respiratory failure due to massive (life-threatening) DAH cannot be excluded. Apparently, standard anti-inflammatory/immunosuppressive therapy with steroids and CYC and/or RTX is sufficient in many or even most patients. On the basis of this analysis, it is my impression that PLEX is not needed for optimal management of DAH in ANCA vasculitis. An exception might be when the severity of the hemorrhage is immediately life threatening and mechanical ventilation is required, where even a minor benefit of PLEX might make a “life or death” difference. PLEX is a reasonably safe procedure, although “anaphylactoid” episodes have been reported (10).

Summary

ANCA vasculitis is a serious and potentially life-endangering disease. Fortunately, modern therapy with combinations of anti-inflammatories (steroid) and immunosuppression (RTX and/or CYC) can most often quickly control the disorder and lead to prolonged disease-free remissions with appropriate maintenance therapy. These regimens are sufficient for the great majority of patients, although benefits of PLEX in small subsets of patients cannot be excluded definitively. Adjunctive use of PLEX is seldom, if ever, needed to manage even very severe kidney disease, and its role in severe DAH is doubtful; however, we lack the necessary hard evidence of a randomized clinical trial with pulmonary-centered end points upon which to rest clinical decision making in difficult cases with life-endangering manifestations.

Disclosures

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Author Contributions

R.J. Glasscock conceptualized the manuscript, was responsible for data curation, wrote the original draft, and reviewed and edited the manuscript.

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See related debate, “Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated Vasculitis (AAV)? PRO,” and commentary, “Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated vasculitis (AAV)? COMMENTARY,” on pages 776–778 and 782–783, respectively.