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

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Introduction

"To plasmapherese (PLEX) or not to PLEX" is a question in the induction therapy for patients with ANCA-associated vasculitis (1). Drs. Glassock and Derebail present differing yet sometimes overlapping conclusions to this question in their virtual debate. Their erudite analysis carefully examines the available literature from their respective pro or con positions. To focus the issues, let us consider three real-life patients who illustrate the quandary of when, or whether, PLEX should be used.

Diffuse Pulmonary Hemorrhage in a 32 Year Old

A 32-year-old mother of three is coughing up blood in the emergency room, complaining of worsening fatigue over the past 3 weeks. Physical examination 7 months prior was unremarkable; hemoglobin was 12.8 mg/dl, and serum creatinine was 0.7 mg/dl. Urinalysis was not performed. She describes new, dark, "tea-colored" urine over the past 2 days. Urinalysis shows numerous red blood cells and red cell casts. Kidney biopsy reveals pauci-immune necrotizing and crescentic glomerulonephritis (GN) with necrosis and crescents in three of seven glomeruli. There is minimal or no interstitial infiltrate, fibrosis, or tubular atrophy. Myeloperoxidase (MPO) ANCA is positive at a titer of 93 (normal <20). High-resolution chest computed tomography reveals diffuse alveolar infiltrates with minimal bronchial abnormalities involving multiple lung lobes. Oxygen saturation is 88% on 2 L of oxygen. The diagnosis is MPO ANCA with diffuse alveolar hemorrhage and necrotizing and crescentic GN. In addition to glucocorticoids and intravenous cyclophosphamide/rituximab, would you order plasmapheresis?

Dr. Derebail would argue that this patient should receive plasmapheresis. Dr. Glassock specifies that no randomized, controlled trials of PLEX as therapy for diffuse alveolar hemorrhage are available and concludes that "PEXIVAS is not very informative regarding the utility of PLEX in treating DAH [diffuse alveolar hemorrhage]. Even a minor benefit of PLEX might make a life-or-death difference." Lung hemorrhage remains a category 1 indication by the American Society of Apheresis. I concur. This 32 year old is in trouble, and plasmapheresis may help. In real life, it did help. The patient received aggressive PLEX and is alive and well two decades later with no long-term sequelae of her pulmonary hemorrhage or necrotizing and crescentic GN.

Ascertaining the severity of pulmonary bleeding is difficult. There must be significant bleeding to observe hemoptysis, and radiographic studies provide suboptimal measures for the severity of pulmonary hemorrhage. The bottom line is plasmapherese this 32 year old with pulmonary bleeding.

Proteinase 3 ANCA Vasculitis, Respiratory Tract Disease, and Acute on Chronic Glomerulosclerosis

A 64-year-old man has known proteinase 3 ANCA GN and upper respiratory tract disease. Rituximab and glucocorticoids were deemed appropriate therapy for his classic upper respiratory disease. Over the past 5 weeks, the serum creatinine increased from 1.3 to 4.4 mg/dl. He now complains of worsening sinusitis and nasal crusting with no other manifestations of vasculitis. Urinalysis reveals glomerular hematuria and some red cell casts. He is admitted to the hospital. Kidney biopsy reveals 15 glomeruli—five are globally sclerotic, three have segmental glomerulosclerosis, three are normal, and the remainder show karyorrhectic debris indicative of active disease. Several glomeruli have fibrotic cellular crescents and no active cellular crescents. Another segment of the cortex reveals significant interstitial fibrosis and tubular atrophy. Serum creatinine continued to rise, and given his uremic symptoms, hemodialysis was initiated. Should this patient receive plasmapheresis?

Neither Dr. Glassock nor Dr. Derebail recommend plasmapheresis in this patient, albeit for different reasons. This patient has AKI on top of chronic disease. Kidney biopsy revealed chronic disease with significant interstitial fibrosis, tubular atrophy, glomerulosclerosis, and fibrocellular crescents—important independent predictors of treatment response1–4(2). Any immunomodulatory therapy—whether glucocorticoids, cyclophosphamide, rituximab, or PLEX—should be scrutinized when it is unlikely that patients will have a long-term dialysis-free outcome. Arguably, minimizing immunosuppression could reduce infectious complications, especially in patients receiving dialysis.

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In this case, the patient has "AKI," but the horse is now out of the barn. He did not receive plasmapheresis, but he is doing well after receiving a kidney transplant.

Rapidly Progressive GN

A 63-year-old man has a 4-week rise in his serum creatinine from 0.9 to 6.2 mg/dl. The patient came to clinical attention because of a purpuric rash on his lower extremity determined to be a leukocytoclastic vasculitis on skin biopsy. Dermatology also obtained a patient history of dark-colored urine and referred the patient to a nephrologist. On presentation to nephrology, the patient was hypertensive with a fading skin rash on a low-dose glucocorticoid regimen. MPO ANCA was positive; other serologies were unremarkable. Urinalysis revealed numerous acanthocytes and red blood cell casts. Kidney biopsy revealed ten glomeruli with necrotizing lesions, three of which showed cellular crescents. Minimal interstitial fibrosis with tubular atrophy was observed. In addition to glucocorticoids, cyclophosphamide, and/or rituximab, should this patient receive PLEX?

It is difficult to determine whether this individual would benefit from the addition of PLEX to the therapeutic armamentarium with the existing data. The discussants diverge on their interpretation of the recent "Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis" (PEXIVAS) study. Kidney biopsy was not an inclusion criterium for the PEXIVAS study, and just over 50% of patients actually had kidney biopsy. In the patients who did, it is unclear when the biopsy was performed relative to their presentation. Dr. Glassock points out that the degree of acute and chronic changes should be equal in both the PLEX and non-PLEX groups because in this large study, randomization would likely balance any differences. Dr. Derebail rebuts this point, asserting that patients in PEXIVAS could have presented with kidney injury due to either advanced sclerosis or acute inflammation. The earlier "Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis" (MEPEX) trial (3) suggested a benefit to PLEX compared with the methylprednisolone arm at 12 months. No randomized, controlled trial concentrates on the subset of patients who have rapidly progressive GN (RPGN) because of acute and aggressive disease with minimal scarring. This aggressive inflammation with amplification of the innate immune response grinds away at glomeruli and the tubulointerstitial compartment, resulting in scarring. Glucocorticoids and agents such as cyclophosphamide have a reasonably rapid onset. The argument for plasmapheresis is to eliminate the adaptive component of this autoimmune response—that is, the autoantibody—with the aim of ameliorating the disease process. An agent that interferes with innate immunity is needed, and the jury is still out on whether Avacopan (the C5a receptor antagonist) is a critical ingredient in the therapeutic armamentarium (4). Whether PLEX would help this 62-year-old man remains unclear until the kidney biopsy data in the PEXIVAS trial are presented. Specifically, how many patients had advanced scarring, and how many had acute injury with minimal interstitial scarring? I would discuss with this 62-year-old man the chance that plasmapheresis could remove the MPO ANCA, allowing cyclophosphamide or rituximab time to work more fully.

This patient did not receive plasmapheresis, and he continues to have a creatinine in the mid–2-mg/dl range and remains on regular maintenance therapy with rituximab. Whether PLEX would or would not help in his long-term course remains uncertain.

My bottom line is (*1*) plasmapheresis for those who you think have diffuse alveolar hemorrhage, (2) avoid plasmapheresis for the majority of patient with AKI on dialysis, and (*3*) consider plasmapheresis in cases of RPGN with acute disease and minimal interstitial fibrosis and tubular atrophy.

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Author Contributions

R.J. Falk wrote the original draft and reviewed and edited the manuscript.

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See related debates, "Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated Vasculitis (AAV)? PRO," and "Should PLEX Be Used for Severe AKI and/or Pulmonary Hemorrhage in ANCA-Associated Vasculitis (AAV)? CON," on pages 776–778 and 779–781, respectively.