Plasma Exchange in ANCA-Associated Vasculitis

Subjects: Allergy

Contributor: Stathis Tsiakas

Therapeutic plasma exchange (TPE) is an adjunctive intervention to immunosuppression for the treatment of severe renal involvement or lung hemorrhage in patients with ANCA-associated vasculitis (AAV). The potential pathogenicity of ANCA makes TPE a reasonable treatment approach for the life-threatening complications of AAV. The largest clinical trial to date, PEXIVAS, failed to demonstrate a clear benefit for TPE in severe AAV. The role of TPE remains controversial across the medical vasculitis community.

Keywords: plasma exchange ; plasmapheresis ; ANCA-associated vasculitis ; kidney disease

1. Introduction

Therapeutic plasma exchange (TPE) is an extracorporeal procedure in which plasma is separated from other blood constituents and subsequently removed from the patient in replacement of fresh frozen plasma or albumin solutions. The fundamental rationale for TPE lies in the removal of a circulating pathogenic factor, namely an antibody, an immune complex, or a monoclonal protein. This therapeutic potential has led to the use of TPE in a number of autoimmune neurologic, hematologic, and renal disorders [1][2][3][4][5]. In addition to TPE, concomitant immunosuppressive treatment is typically applied in these cases as a means to prevent the production of the culprit immune factor. The level of evidence for therapeutic apheresis varies considerably depending on the disease. Evidence-based clinical guidelines covering common indications, graded by strength of evidence and recommendation, are provided by the American Society for Apheresis (ASFA) guidelines [6].

ANCA-associated vasculitis (AAV) is a systemic disease characterized by destructive inflammation of small- to medium-sized blood vessels in the presence of circulating ANCA [7]. Despite the introduction of immunosuppressive agents since the 1970s, major organ involvement, including kidney and lung, is still related to a significant mortality ratio compared to the general population [8][9]. Given the immunologic nature of AAV, plasma exchange has been applied as an adjunct therapy in patients with active, severe renal disease or diffuse alveolar hemorrhage. A number of clinical studies throughout the years have provided information about the efficacy of TPE in AAV, though with ambiguous outcomes for renal and patient prognosis [10][11][12][13][14][15][16][17][18]. Since TPE is an invasive method of treatment, occasionally complicated by bleeding disorders, infections, hypotension, or anaphylactic reactions, there is an increased need for concrete evidence regarding the use of TPE in AAV [19][20].

2. Pathogenetic Rationale for Plasma Exchange in ANCA-Associated Vasculitis

Antineutrophilic cytoplasmic antibodies (ANCA) are mainly immunoglobulin G (IgG) antibodies detected by indirect immunofluorescence or an enzyme-linked immunosorbent assay [21]. The two major antigens targeted by ANCA are proteinase 3 (PR3) and myeloperoxidase (MPO), which are expressed in the neutrophil primary granules and the monocytes. The presumed pathogenetic mechanism of ANCA-induced inflammatory tissue injury includes the binding of ANCA to primed neutrophils, leading to neutrophil degranulation and activation of the alternative complement pathway [22][23]. Several studies in animal models have shown that ANCA apart from potential biomarkers have an actual pathogenetic role in the disease. Specifically, Xiao et al. reported that the infusion of splenocytes from immunized MPO knockout mice or purified anti-MPO IgG antibodies into wild-type mice resulted in the development of severe necrotizing and crescentic glomerulonephritis with a paucity of glomerular immune deposits [24]. In another study, all immunized Wistar Kyoto rats with human MPO developed crescentic glomerulonephritis and lung hemorrhage [25]. Of note, a case of human transplacental transfer of MPO antibodies from a mother to the fetus has been described, causing lung hemorrhage to the neonate [26]. Based on the aforementioned evidence, a direct relationship between ANCA and active disease was suggested.

Considering the pathogenetic essence of ANCA, the removal of these antibodies may exert a beneficial effect on the disease. Immunoglobulin G has a half-life of approximately 21 days; depletion of the serum IgG antibody levels solely by halting their production with immunosuppressive agents would require at least several weeks. TPE offers the possibility of rapidly removing these pathogenic antibodies from the patients' plasma when added to the standard immunosuppressive regimen. Both common techniques of TPE, centrifugal apheresis and membrane plasma separation, are effective in removing IgG molecules. Due to extravascular distribution, one day intervals between TPE sessions are commonly applied in order to allow immunoglobulins to further redistribute into the vascular space; exceptions to this practice include emergency care circumstances where daily sessions are required, e.g., pulmonary hemorrhage [27][28]. Besides antibody elimination, other putative beneficial mechanisms of action of TPE include the removal of inflammatory mediators, such as cytokines and complement components, and the replenishment of plasma factors via fresh frozen plasma infusion, such as factor H [29].

3. Current Clinical Indications for Plasma Exchange in ANCA-Associated Vasculitis

AAV comprises a group of systemic disorders that share a common pathology of pauci-immune necrotizing inflammation of small vessels, resulting in tissue injury and multiple organ involvement. According to the 2012 Revised International Chapel Hill Consensus Conference, AAV is classified into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [30]. Clinical features may overlap between these entities, especially MPA and GPA. EGPA rarely involves the kidney and is distinguished by the presence of eosinophilia and asthma [31].

Kidney disease at diagnosis is common (70% and 90% in GPA and MPA, respectively) and is an important prognostic factor for patient survival. An estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at presentation correlates with a 50% risk of ESKD or death at 5 years. The typical renal lesion is that of a necrotizing crescentic glomerulonephritis with little or no immune complex deposition, manifesting as a rapid decline in kidney function with proteinuria and active urine sediment. Lungs are also frequently involved, especially in GPA. Diffuse alveolar hemorrhage is a serious complication associated with an increased risk of death, affecting approximately 10% of patients. Before the introduction of immunosuppressive agents, up to 90% of patients died within two years of AAV diagnosis. Cyclophosphamide along with high-dose corticosteroids significantly reduced mortality, although it was associated with serious adverse events, namely infections and malignancy [9][32][33].

Treatment with TPE may play a role in refractory AAV, as defined by the lack of response after at least 4 weeks of standard immunosuppressive regimens and following the exclusion of other factors that may affect treatment response, including nonadherence, infection, and chronic organ damage [34].

4. PEXIVAS Trial

Given the lack of available high-quality data regarding the efficacy and safety of adjunct TPE and the increased incidence of ESKD or death despite advances in immunosuppressive therapy, the multicenter randomized PEXIVAS trial was conducted to evaluate the use of TPE in patients who present with severe AAV, as defined by an eGFR < 50 mL/min/1.73m^2 or diffuse alveolar hemorrhage. The trial had a two-by-two factorial design; randomization included initial treatment with seven sessions of TPE within 14 days or no TPE and a standard-dose glucocorticoid regimen versus a reduced-dose regimen. The primary outcome was death from any cause or ESKD. Patients received either cyclophosphamide or rituximab as induction therapy and one of the two different regimens of oral glucocorticoids. Pulses of intravenous methylprednisolone (1–3 g) were given to all patients. Azathioprine was used as maintenance therapy after induction with cyclophosphamide. Patients in the TPE arm received albumin as a replacement solution, with fresh frozen plasma used only for the final portion of the replacement if bleeding diathesis was present. Additional TPE sessions for ongoing signs and histological evidence of disease activity or serological biomarkers (e.g., elevated ANCA titers) were not permitted.

5. The Role of Plasma Exchange in ANCA-Associated Vasculitis after PEXIVAS Trial

The results of the PEXIVAS trial created controversy across the medical community regarding the role of TPE in severe AAV [35][36][37][38][39][40]. The study included the largest patient population to date with a multinational enrollment, which allows for a broad generalizability of the results. However, several limitations of potential clinical significance arose after careful review.

Kidney biopsy was not a requirement at entry, and while most patients had one, analysis of the existing histologic data has not yet been performed to investigate the degree of activity with the response to TPE. Considering, for instance, that patients with MPO-ANCA vasculitis occasionally follow a slowly progressive course and exhibit significant chronic lesions at diagnosis, TPE would not be expected to offer an additional advantage. Another concern is the broad range of renal impairment (eGFR < 50 mL/min/1.73 m^2) that was allowed in the study. As shown by previous clinical trials, TPE primarily favors those with severe active renal disease at presentation. Subgroup analysis of the primary outcome showed that TPE offered a nominal benefit in patients with a serum creatinine level > 5.7 mg/dL or those requiring dialysis (HR 0.77, CI 0.53–1.11). In view of the marked improvement in the renal outcomes of patients with similar presentation and biopsy-proven AAV shown in the MEPEX trial, TPE may have a favorable effect in subjects who present with severe renal impairment.

Of note, the survival analysis in the PEXIVAS trial showed an advantage, albeit non-significant, of TPE in the first year regarding the primary outcome. Since TPE is a brief intervention of the induction therapy, improvement is anticipated in a short period of time after treatment. Other factors may influence the course of the disease in the long term. With respect to lung hemorrhage, a nominal benefit of TPE was observed in the trial (HR 0.64, CI 0.33–1.24 for nonsevere hemorrhage, HR 0.67, CI 0.28–1.64 for severe hemorrhage). An issue to be considered is if the power of the study was high enough to exhibit a significant effect in subjects with the most severe clinical manifestations. Selection bias may have affected the relatively low recruitment of patients with severe diffuse alveolar hemorrhage in the trial since many physicians would hesitate not to use TPE in this population. Given the low proportion of patients with severe pulmonary hemorrhage and the associated high mortality, TPE may still have a role in the management of this life-threatening complication.

The PEXIVAS trial undoubtedly enriched the existing knowledge with useful information about the initial management of patients with severe AAV. Despite the reported neutral effect of TPE, other important implications for the attending physicians also came to light. The use of TPE was not associated with more serious adverse events, including infections, as shown by previous studies. Given the potential benefit in selected subgroups with severe renal or pulmonary disease and the lack of undesired effects, TPE will likely continue to be a part of the treatment armamentarium for many specialists. Moreover, the trial demonstrated that the use of a reduced-dose glucocorticoid regimen was safer and equally effective. Lastly, it is plausible that more evidence from PEXIVAS will emerge in the future, as further analysis of the data (e.g., kidney biopsy evaluation) may provide additional insights about the utility of TPE in specific subsets of patients.

References

1. Zanatta, E.; Cozzi, M.; Marson, P.; Cozzi, F. The role of plasma exchange in the management of autoimmune disorders. Br. J. Haematol. 2019, 186, 207–219.
2. Kiprov, D.D.; Hofmann, J.C. Plasmapheresis in immunologically mediated polyneuropathies. Ther. Apher. Dial. 2003, 7, 189–196.
3. Clark, W.F.; Stewart, A.K.; Rock, G.A.; Sternbach, M.; Sutton, D.M.; Barret, B.J.; Heidenheim, A.P.; Garg, A.X.; Churchill, D.N. Plasma exchange when myeloma presents as acute renal failure: A randomized, controlled trial. Ann. Intern. Med. 2005, 143, 777–784.
4. Pusey, C.D.; Levy, J.B. Plasmapheresis in immunologic renal disease. Blood Purif. 2012, 33, 190–198.
5. Cataland, S.R.; Wu, H.M. Diagnosis and management of complement mediated thrombotic microangiopathies. Blood Rev. 2014, 28, 67–74.
6. Padmanabhan, A.; Connelly-Smith, L.; Aqui, N.; Balogun, R.A.; Klingel, R.; Meyer, E.; Pham, H.P.; Schneiderman, J.; Witt, V.; Wu, Y.; et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. J. Clin. Apher. 2019, 34, 171–354.
7. Geetha, D.; Jefferson, J.A. ANCA-Associated Vasculitis: Core Curriculum 2020. Am. J. Kidney Dis. 2020, 75, 124–137.
8. Hilhorst, M.; Wilde, B.; van Paassen, P.; Winkens, B.; van Breda Vriesman, P.; Cohen Tervaert, J.W. Improved outcome in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis: A 30-year follow-up study. Nephrol. Dial. Transplant. 2013, 28, 373–379.
9. Flossmann, O.; Berden, A.; de Groot, K.; Hagen, C.; Harper, L.; Heijl, C.; Höglund, P.; Jayne, D.; Luqmani, R.; Mahr, A.; et al. Long-term patient survival in ANCA-associated vasculitis. Ann. Rheum. Dis. 2011, 70, 488–494.
10. Pusey, C.D.; Rees, A.J.; Evans, D.J.; Peters, D.K.; Lockwood, C.M. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int. 1991, 40, 757–763.

11. Zäuner, I.; Bach, D.; Braun, N.; Krämer, B.K.; Fünfstück, R.; Helmchen, U.; Schollmeyer, P.; Böhler, L. Predictive value of initial histology and effect of plasmapheresis on long-term prognosis of rapidly progressive glomerulonephritis. Am. J. Kidney Dis. 2002, 39, 28–35.
12. Frascà, G.M.; Soverini, M.L.; Falaschini, A.; Tampieri, E.; Vangelista, A.; Stefoni, S. Plasma exchange treatment improves prognosis of antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis: A case-control study in 26 patients from a single center. Ther. Apher. Dial. 2003, 7, 540–546.
13. Solar-Cafaggi, D.; Atisha-Fregoso, Y.; Hinojosa-Azaola, A. Plasmapheresis therapy in ANCA-associated vasculitides: A single-center retrospective analysis of renal outcome and mortality. J. Clin. Apher. 2016, 31, 411–418.
14. Walsh, M.; Merkel, P.A.; Peh, C.A.; Szpirt, W.M.; Puéchal, X. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N. Engl. J. Med. 2020, 382, 622–631.
15. Jayne, D.R.; Gaskin, G.; Rasmussen, N.; Abramowicz, D.; Ferrario, F.; Guillevin, L.; Mirapeix, E.; Savage, C.O.; Sinico, R.A.; Stegeman, C.A.; et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J. Am. Soc. Nephrol. JASN 2007, 18, 2180–2188.
16. Klemmer, P.J.; Chalermskulrat, W.; Reif, M.S.; Hogan, S.L.; Henke, D.C.; Falk, R.J. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am. J. Kidney Dis. 2003, 42, 1149–1153.
17. Szpirt, W.M.; Heaf, J.G.; Petersen, J. Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis—A clinical randomized controlled trial. Nephrol. Dial. Transplant. 2011, 26, 206–213.
18. Gregersen, J.W.; Kristensen, T.; Krag, S.R.; Birn, H.; Ivarsen, P. Early plasma exchange improves outcome in PR3-ANCA-positive renal vasculitis. Clin. Exp. Rheumatol. 2012, 30 (Suppl. S70), S39–S47.
19. Kiprov, D.D.; Golden, P.; Rohe, R.; Smith, S.; Hofmann, J.; Hunnicutt, J. Adverse reactions associated with mobile therapeutic apheresis: Analysis of 17,940 procedures. J. Clin. Apher. 2001, 16, 130–133.
20. Chirnside, A.; Urbaniak, S.J.; Prowse, C.V.; Keller, A.J. Coagulation abnormalities following intensive plasma exchange on the cell separator. II. Effects on factors I, II, V, VII, VIII, IX, X and antithrombin III. Br. J. Haematol. 1981, 48, 627–634.
21. Bossuyt, X.; Cohen Tervaert, J.W.; Arimura, Y.; Blockmans, D.; Flores-Suárez, L.F.; Guillevin, L.; Hellmich, B.; Jayne, D.; Jennette, J.C.; Kallenberg, C.G.M.; et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat. Rev. Rheumatol. 2017, 13, 683–692.
22. Nakazawa, D.; Masuda, S.; Tomaru, U.; Ishizu, A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat. Rev. Rheumatol. 2019, 15, 91–101.
23. Jennette, J.C.; Falk, R.J. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. Nat. Rev. Rheumatol. 2014, 10, 463–473.
24. Xiao, H.; Heeringa, P.; Hu, P.; Liu, Z.; Zhao, M.; Aratani, Y.; Maeda, N.; Falk, R.J.; Jennette, J.C. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J. Clin. Investig. 2002, 110, 955–963.
25. Little, M.A.; Smyth, L.; Salama, A.D.; Mukherjee, S.; Smith, J.; Haskard, D.; Nourshargh, S.; Cook, H.T.; Pusey, C.D. Experimental autoimmune vasculitis: An animal model of anti-neutrophil cytoplasmic autoantibody-associated systemic vasculitis. Am. J. Pathol. 2009, 174, 1212–1220.
26. Bansal, P.J.; Tobin, M.C. Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. Ann. Allergy Asthma Immunol. 2004, 93, 398–401.
27. Reverberi, R.; Reverberi, L. Removal kinetics of therapeutic apheresis. Blood Transfus. = Trasfus. Sangue 2007, 5, 164–174.
28. Williams, M.E.; Balogun, R.A. Principles of separation: Indications and therapeutic targets for plasma exchange. Clin. J. Am. Soc. Nephrol. CJASN 2014, 9, 181–190.
29. Chen, S.F.; Wang, F.M.; Li, Z.Y.; Yu, F.; Chen, M.; Zhao, M.H. Complement Factor H Inhibits Anti-Neutrophil Cytoplasmic Autoantibody-Induced Neutrophil Activation by Interacting with Neutrophils. Front. Immunol. 2018, 9, 559.
30. Jennette, J.C.; Falk, R.J.; Bacon, P.A.; Basu, N.; Cid, M.C.; Ferrario, F.; Flores-Suarez, L.F.; Gross, W.L.; Guillevin, L.; Hagen, E.C.; et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013, 65, 1–11.
31. Gioffredi, A.; Maritati, F.; Oliva, E.; Buzio, C. Eosinophilic granulomatosis with polyangiitis: An overview. Front. Immunol. 2014, 5, 549.
32. Binda, V.; Moroni, G.; Messa, P. ANCA-associated vasculitis with renal involvement. J. Nephrol. 2018, 31, 197–208.

33. Kamesh, L.; Harper, L.; Savage, C.O. ANCA-positive vasculitis. J. Am. Soc. Nephrol. JASN 2002, 13, 1953–1960.
34. Yates, M.; Watts, R.A. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann. Rheum. Dis. 2016, 75, 1583–1594.
35. Esposito, P.; Cipriani, L.; Viazzi, F. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N. Engl. J. Med. 2020, 382, 2168–2169.
36. Derebail, V.K.; Falk, R.J. ANCA-Associated Vasculitis—Refining Therapy with Plasma Exchange and Glucocorticoids. N. Engl. J. Med. 2020, 382, 671–673.
37. De Vriese, A.S.; Fervenza, F.C. PEXIVAS: The End of Plasmapheresis for ANCA-Associated Vasculitis? Clin. J. Am. Soc. Nephrol. 2021, 16, 307–309.
38. Cortazar, F.B.; Niles, J.L. The Fate of Plasma Exchange and Glucocorticoid Dosing in ANCA-Associated Vasculitis after PEXIVAS. Am. J. Kidney Dis. 2020, 76, 595–597.
39. Hohenstein, B.; Schettler, V. With reasonable doubt: Plasma exchange in PEXIVAS. Ther. Apher. Dial. 2021, 25, 128–129.
40. Prendecki, M.; McAdoo, S.P.; Pusey, C.D. Is There a Role for Plasma Exchange in ANCA-Associated Vasculitis? Curr. Treat. Options Rheumatol. 2020, 6, 313–324.
