Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2022.09719
Ulus Romatol Derg 2022;14(3):131-136

Plasma exchange therapy in ANCA-associated vasculitis: A single-center retrospective cohort study

ANCA ile ilişkili vaskülitte plazma değişim tedavisi: Tek merkez retrospektif kohort çalışması

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Abstract

Objective: Meta-analysis of randomized controlled trials showed that plasma exchange (PLEX) has no significant effect on mortality and reduces the 12-month risk of end-stage kidney disease at the cost of increasing the risk of serious infections in patients with ANCA-associated vasculitis (AAV).

Methods: We retrospectively reviewed patient charts who underwent PLEX therapy between October 2013 and March 2022 in our apheresis unit. Patients who were under 18 and underwent PLEX therapy for non-rheumatic and rheumatic diseases other than AAV were excluded. We collected all information regarding the primary indication of PLEX therapy, procedure details, concomitant immunosuppressives, overall survival, outcomes of organ involvement, and complications related to PLEX therapy.

Results: Twenty-eight patients (Male/Female: 18/10) with AAV were evaluated. Diffuse alveolar hemorrhage (DAH) was the primary indication for PLEX therapy in 6 (21%) patients [myeloperoxidase (MPO)/proteinase-3 (PR-3): 1/5], kidney involvement and/or DAH in 22 (79%) (MPO/PR-3: 10/11). Overall, there were 16 (57%) severe/opportunistic infections and 5 (18%) deaths within the first three months. One (4%) severe infection (COVID-19) and 3 (11%) deaths were observed between 3 and 12 months. Overall, 10 (45%) patients were hemodialysis-dependent at month three, and there were no additional dialysis-dependent patients in the 12th month.

Conclusion: most infections and deaths occurred within the first three months of PLEX therapy. The renal outcome was poor in patients with high-risk baseline creatinine levels (≥5.8 mg/dL). Despite this, having no new dialysis-dependent patients between 3 and 12 months suggests that PLEX still can be an option as an adjunct therapy, especially in some subgroups of AAV patients in daily practice.

Keywords: Plasma exchange, plasmapheresis, anti-neutrophil cytoplasmic antibody-associated vasculitis, organ damage, opportunistic infections, immunosuppressive agents

Öz

Amaç: Randomize kontrollü çalışmaların meta analizi, plazma değişiminin (PLEX) mortalite üzerinde anlamlı bir etkisinin olmadığını ve ANCA-ilişkili vaskülit (AAV) hastalarında ciddi enfeksiyon riskini artırma pahasına 12 aylık son dönem böbrek hastalığı riskini azalttığını göstermiştir.

Yöntem: Aferez ünitemizde Ekim 2013-Mart 2022 tarihleri arasında PLEX tedavisi uygulanan hastaların dosya kayıtları retrospektif olarak incelendi. On sekiz yaş altı ve romatizmal olmayan hastalıkları ve AAV dışındaki romatizmal hastalıkları nedeniyle PLEX tedavisi alan hastalar çalışma dışı bırakıldı. PLEX tedavisinin birincil endikasyonu, işlem detayları, eşlik eden immünosüpresifler, genel sağkalım, organ tutulumunun sonuçları ve PLEX tedavisi ile ilgili komplikasyonlarla ilgili tüm bilgiler toplandı.

Bulgular: AAV'li 28 hasta (Erkek/Kadın: 18/10) değerlendirildi. Diffüz alveoler hemoraji (DAH) 6 (%21) hastada [miyeloperoksidaz (MPO)/proteinaz-3 (PR-3): 1/5], böbrek tutulumu ve/veya DAH 22 (%79) hastada PLEX tedavisinin birincil endikasyonuydu (MPO/PR-3: 10/11). Genel olarak, ilk üç ayda 16 (%57) ciddi/fırsatçı enfeksiyon ve 5 (%18) ölüm meydana geldi. Üç ila 12 ay arasında bir (%4) ciddi enfeksiyon (COVID-19) ve 3 (%11) ölüm gözlemlendi. Genel olarak, 10 (%45) hasta üçüncü ayda hemodiyaliz bağımlıydı ve 12. ayda başka diyalize bağımlı hasta olmadı.

Sonuç: Enfeksiyonların ve ölümlerin çoğu, PLEX tedavisinin ilk üç ayında meydana geldi. Yüksek riskli başlangıç kreatinin düzeyleri (≥5,8 mg/dL) olan hastalarda renal sonuç kötüydü. Buna rağmen 3 ile 12. aylık süre arasında yeni diyaliz hastasının gelişmemesi bize günlük pratikte bazı alt grup hastalarda PLEX tedavisinin hala yardımcı tedavi olarak tercih edilebileceğini düşündürmüştür.

Anahtar Kelimeler: Plazma değişimi, plazmaferez, anti-nötrofil sitoplazmik antikorla ilişkili vaskülit, organ hasarı, fırsatçı enfeksiyonlar, immünosüpresif ajanlar

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Received / Geliş Tarihi: 02.12.2022 **Accepted / Kabul Tarihi:** 08.12.2022

Cite this article as / Atıf: Özgüler Y, Ak T, Esatoğlu SN, Elverdi T, Eşkazan AE, Uğurlu S, Hatemi G, Seyahi E, Melikoğlu M, Fresko İ, Ar MC, Hamuryudan V. Plasma exchange therapy in ANCA-associated vasculitis: A single-center retrospective cohort study. Ulus Romatol Derg 2022;14(3):131-136

Introduction

Plasma exchange (PLEX) is the separation of the plasma from the cellular components of the blood by an extracorporeal system and its replacement with fresh frozen plasma (FFP) and/or albumin. Therefore, harmful immunoglobulins, immune complexes, complement components, and cytokines, which have a role in the disease process, are rapidly removed from the circulation. Since PLEX is a relatively invasive and difficult to access treatment modality high costs, it is mostly used as a salvage treatment in critically ill patients with rheumatic disorders who do not respond adequately to other immunosuppressive treatments [e.g., pulse steroid, cyclophosphamide (CYC), or rituximab (RTX)].[1] The main indications of PLEX in rheumatic diseases are as follows: ANCA-associated vasculitis (AAV), systemic lupus erythematosus, catastrophic antiphospholipid syndrome, cryoglobulinemic vasculitis, Goodpasture syndrome, and scleroderma renal crisis.[2-4]

A recently published systematic review/meta-analysis of randomized controlled trials (RCTs) found that PLEX reduced the 12-month risk of end stage kidney disease, increased the risk of serious infections in patients with AAV, had no significant impact on mortality.[1] The most important complication attributed to PLEX appears to be infections, which often occur early, and both primary pathogens (e.g., bacteria) and opportunistic organisms (e.g., PJ, CMV, or Candida spp.) may be responsible for these infections.[1,5-7] The increased risk of infection has been attributed to the removal of antibodies and complement proteins from the circulation. However, the fact that PLEX causes infection at a lower rate in non-rheumatic diseases (e.g., thrombotic thrombocytopenic purpura, autoimmune encephalitis) suggests that aggressive immunosuppressive treatment and severe organ dysfunction in critical rheumatic diseases play an important role in the development of infections.[8,9]

Given that the meta-analysis only included RCTs, it has some limitations, such as the lack of data informing potential subgroup effects and clinical heterogeneity across studies, which make the results difficult to be generalized and/or lead to underestimation of a treatment alternative that might be beneficial in a subgroup of patients.

The aim of this real-life setting study was to retrospectively analyze the efficacy of PLEX in patients with AAV in terms of overall survival, causes of death, and renal survival along with infectious or non-infectious complications.

Materials and Methods

We retrospectively reviewed the charts of patients who underwent PLEX between October 2013 and March 2022 in the Apheresis Unit of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine. Patients who were under 18 and had non-rheumatic diseases (e.g., thrombotic thrombocytopenic purpura, multiple sclerosis, or hyperviscosity syndrome) or rheumatic diseases other than AAV were excluded. We evaluated the period from when the patients received PLEX therapy to the last visit date. Information regarding the underlying rheumatic disease, the primary indication of PLEX therapy, details of the procedure (type of replacement fluid: Albumin and/or FFP; type of venous access: peripheral vein vs. central venous catheters, and the number of PLEX cycles), concomitant use of immunosuppressives e.g., corticosteroids, CYC, RTX, or intravenous immunoglobulin (IVIG), overall survival, organ involvement, and complications related to the PLEX therapy were collected from the patient charts. Death, infections and other complications, including the outcome of organ involvement, were evaluated during the PLEX therapy, and at 3-months and 12-months following PLEX. This study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethical Committee for Clinical Studies (date: 02.06.2022, approval number: 396452).

Statistical Analysis

Descriptive statistics were used to delineate the demographic, baseline and follow-up characteristics of the patients. Data are expressed as means and standard deviations (SD), median values with ranges or frequency (%).

Results

Baseline Characteristics of the Patients

The chart review revealed 318 patients who underwent PLEX therapy from October 2013 to March 2022 in our apheresis unit. After excluding 253 patients with non-rheumatic diseases, 30 patients with rheumatic diseases other than AAV, and 7 patients who were under 18 years old, 28 patients with AAV were included in the study (Figure 1).

Among 28 AAV patients, 10 (36%) were female and 18 (64%) were male. Mean age of the patients was 48.5±14.6 years and the median follow-up starting from PLEX day 1 was 13.5 months (Q1-Q3: 2-28). Myeloperoxidase (MPO) was positive in 11 patients and proteinase-3 (PR3) was positive in 16 patients. One patient was negative for both PR3 and MPO, but his renal biopsy was compatible with AAV.

Diffuse alveolar hemorrhage (DAH) was the primary indication for PLEX therapy in 6 (21%) (MPO/PR-3: 1/5),

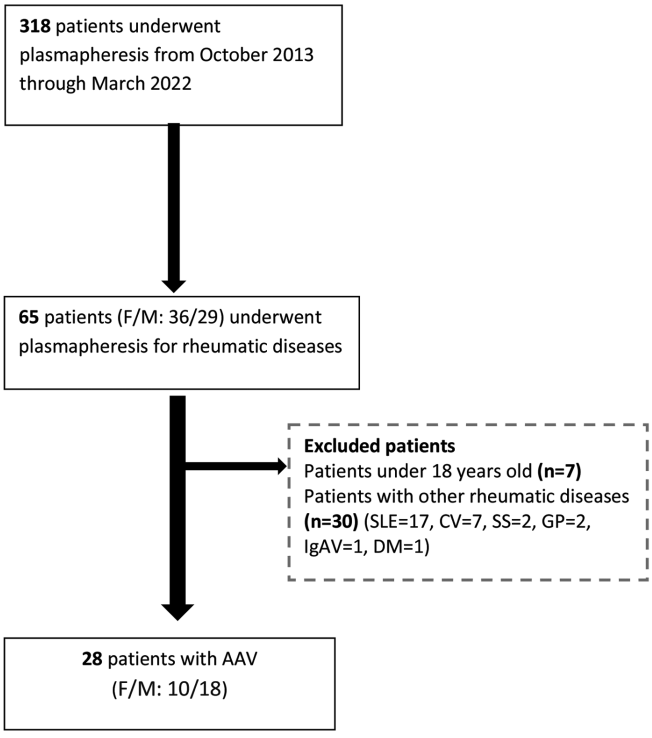

Figure 1. Flow-chart of the included patients

AAV: ANCA-associated vasculitis, SLE: Systemic lupus erythematosus, CV: Cryoglobulinemic vasculitis, SS: Systemic sclerosis, GP: Goodpasture syndrome, IgAV: IgA vasculitis, DM: Dermatomyositis

Table 1. Patients' baseline characteristics and features of PLEX therapy

	Number of patients (28)
Age (mean ± SD)	48.5±14.6
Male gender, n (%)	18 (64%)
Median follow-up, months, (range)	13.5 (2-28)
ANCA positivity, n (%)	27 (95)
PR3, n (%)	16 (57)
MPO, n (%)	11 (39)
Immunosuppressives	
MP+CYC, n (%)	13 (46)
MP+RTX, n (%)	4 (14)
MP+CYC+RTX, n (%)	10 (36)
IVIG, n (%)**	2 (7)
Median (range) n of PLEX sessions	6 (4-7)
Primary indication of PLEX	
DAH, n (%)	6 (21)
Kidney ± DAH, n (%)	22 (79)
PLEX with	
FFP, n (%)	7 (25)
Albumin, n (%)	5 (18)
FFP and albumin, n (%)	16 (57)
Route of venous access	
Peripheral venous, n (%)	11 (39)
Central venous, n (%)	17 (61)

AAV: ANCA-associated vasculitis, CYC: Cyclophosphamide, DAH: Diffuse alveolar hemorrhage, FFP: Fresh frozen plasma, IVIG: Intravenous immunoglobulin, MP: Methylprednisolone, PLEX: Plasma exchange, SD: Standard deviation, RTX: Rituximab

and kidney involvement and/or DAH in 22 (79%) (MPO/PR-3: 10/11). patients (Table 1).

Immunosuppressive treatments used along with PLEX therapy include methylprednisolone (MP)+CYC in 13 (46%), MP+RTX in 4 (14%), and MP+CYC+RTX in 10 (36%) patients. IVIG was used as an adjunct treatment in 1 patient and as a solo treatment in another patient in whom sepsis could not be ruled out (Table 1).

Features of Plasma Exchange Therapy

The median number of PLEX was 6 (range: 4-7) (Table 1). 1.3 plasma volumes were removed per session using a Fresenius Comtec 2010 machine (centrifugal technique) and were replaced with FFP (n=7, 25%), albumin (n=5, 18%), or FFP and albumin (n=16, 57%). Anticoagulant Citrate Dextrose Solution-A was used as the anticoagulant. The procedures were applied every other day, but every day in cases of alveolar hemorrhage, until the stabilization of pulmonary symptoms and/or active hemoptysis. The procedure was performed using a central venous catheter and peripheral veins in 17 (61%) and 11 (39%) patients, respectively.

Outcomes

Death and Infections

Overall, there were 16 (57%) severe/opportunistic infections and 5 (18%) deaths within the first 3 months (Figure 2). One (4%) severe infection (COVID-19) and 3 (11%) deaths were additionally observed between 3 and 12 months after the PLEX.

Among 22 (79%) patients who presented with renal involvement and/or DAH, 15 (68%) developed severe/opportunistic infections within the first three months following the PLEX (Figure 2), including sepsis (n=5, 18%), respiratory tract infections (n=8, 29%), soft tissue infections (n=1, 3%), urinary tract infections (n=1, 3%), and opportunistic infections [n=6, 20%; (CMV infection: n=4, P Pneumocystis jirovecii pneumonia: n=1, fungal infections: n=1)]. Infections were observed in 7 (41%) and 6 (55%) patients of the 17 patients with a central venous catheter, and 11 patients who had a peripheral venous catheter, respectively. Infection rates according to the type of immunosuppressive treatment used were as follows: 8/13 (62%) in MP+CYC+RTX, 6/10 (60%) in MP+CYC, and 1/4 (25%) in MP+RTX group.

Four (18%) patients with renal involvement and/or DAH died within the first 3 months following the PLEX. Three of those patients died while receiving PLEX, and one died 4 weeks after the PLEX. The causes of death were active disease and infection in 3 patients and infection in 1

patient. Additionally, 1 patient had severe infection and 3 (14%) other patients died (disease activation=1, unknown reason=1, and COVID-19=1) after 3 months within the first year follow-up after PLEX.

Among the 6 (21%) patients who presented with isolated DAH, only one patient developed an opportunistic infection (CMV) and died from active disease complicated by this infection within the first 3 months of PLEX (Figure 2). No other deaths were observed in this group at month 12.

Organ Survival

All 12 of the 17 (71%) patients with pulmonary involvement (with or without renal involvement) were at life at month 3 and showed improvement in their lung findings. One patient died of unknown reasons and no other DAH reactivation was observed after 3 months.

The median baseline creatinine level before PLEX was 4.2 mg/dL (range: 3.6-5.3) in 22 patients with renal involvement (with or without DAH). PLEX with concomitant hemodialysis (HD) was initiated in 12 (55%) patients with a mean baseline creatinine level of 5.87±2.5 mg/dL. Overall 10 (45%) patients were HD dependent at month 3 and there were no additional dialysis-dependent patients at month 12. We categorized the patients with renal involvement according to their baseline creatinine levels. Three of the 17 patients (MPO/PR-3: 9/7) with initial creatinine levels between 3.3-5.8 mg/dL (defined as moderate to high-risk group in the recent meta-analysis) died, and 6 were still HD dependent at month 3. Three more patients died during the follow-up within one year while no further cases with HD requirement were observed. The initial creatinine level was ≥5.8 mg/dL (high risk group) in 5 patients (MPO/PR-3: 1/4), four of whom became permanently HD dependent within three months of PLEX. One patient died during follow-up after 3 months (Figure 3).

Discussion

In our retrospective cohort, we found that severe/opportunistic infections and death were more common in AAV patients with renal involvement, similar to other studies. Most infections and deaths occurred within the first 3 months of PLEX therapy. The renal outcome was poor in patients with high-risk baseline creatinine levels (≥5.8 mg/dL).

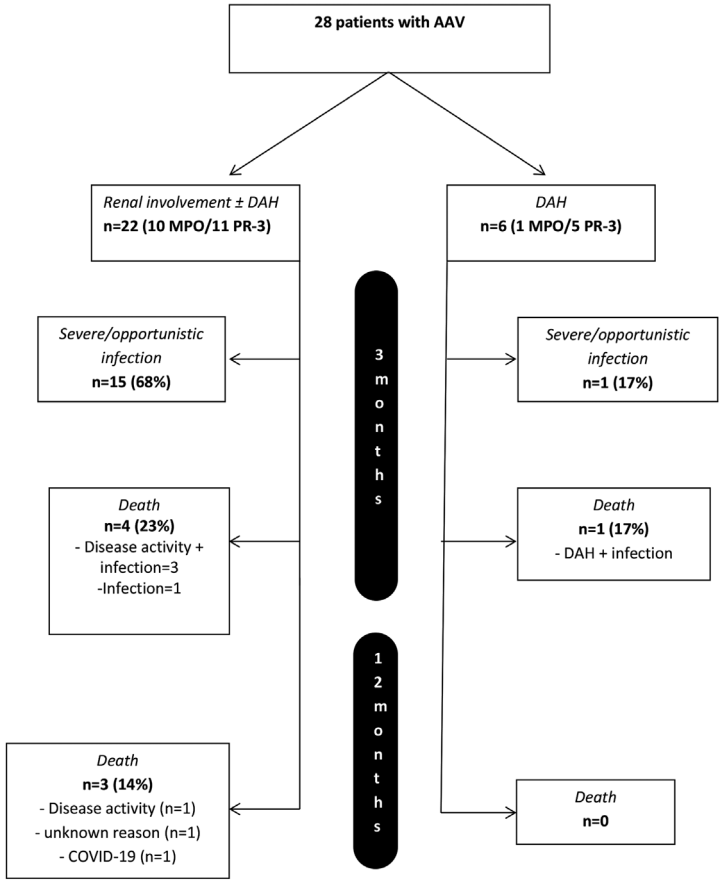

Figure 2. Three and 12-months follow-up of the patients who underwent plasma exchange for AAV
AAV: ANCA-associated vasculitis, MPO: Myeloperoxidase, PR-3: Proteinase-3, DAH: Diffuse alveolar hemorrhage

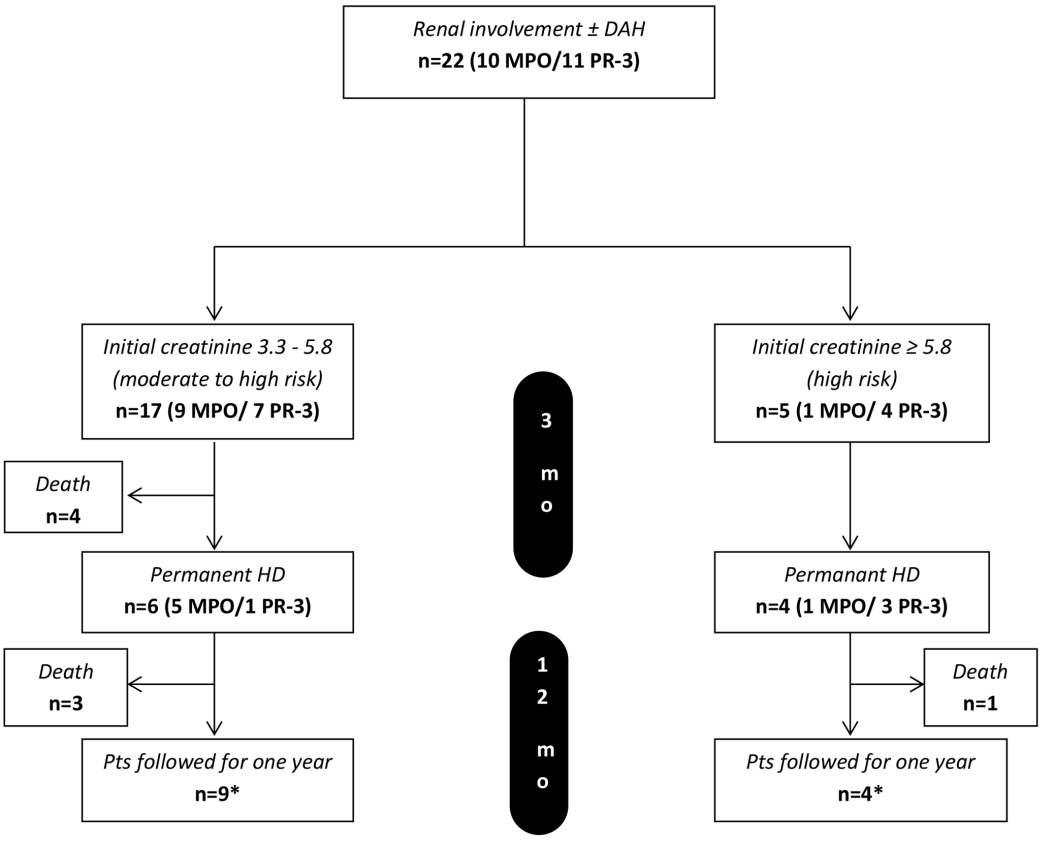

Figure 3. Renal outcomes of patients with AAV

AAV: ANCA-associated vasculitis, MPO: Myeloperoxidase, PR-3: Proteinase-3, DAH: Diffuse alveolar hemorrhage, HD: Hemodialysis
* There was no new HD dependent patients

Of the PR-3-positive 11 patients with renal involvement only 4 (36%) became HD dependent at month 12 while this was the case in 6 out of 10 (60%) patients in the MPO-positive group.

Overall, 57% patients experienced severe infection during the first 3 months after PLEX. This rate seems to be much higher than reported in the RCTs and may be explained by the immunosuppressive treatment regimens used in our cohort. More than one-third of patients in our cohort received a triple combination (MP, CYC and RTX). One might expect higher rates of severe infection with an increasing number of immunosuppressives used in the combination therapy. However, in our hands, infection rates were similar in the MP+CYC+RTX (62%) and MP+CYC (60%) groups. The infection rate was lower (25%) in the MP+RTX group compared these two groups, but also the number of patients (n=4) was low in this group. Furthermore, critically-ill patients who were usually ineligible for RCTs were more likely to be present in our cohort. Of note, in the PEXIVAS trial, which is the largest PLEX study in this field, the number of patients who had DAH or high-risk chronic renal disease was low.[2] The reason for the underrepresentation of critically-ill patients was probably because randomization processes usually take some time, and physicians prefer treating these patients immediately.

Although, severe infections were common in our patients, in 4 of the 5 deaths, the underlying cause was primarily the active rheumatic disease and infection was a subsidiary reason. Infection was the primary cause of death in only a patient within the first 3 months of follow-up. Permanent renal damage and HD dependency were observed within the first 3 months of PLEX and not after that. This is an important finding, hence HD dependency in AAV patients has been associated with increased risk of infection. Even though the risk of infection is high within the first three months, PLEX might still be a considerable option given that the infection-related mortality rate and the risk of developing HD dependency is relatively low in patients who survive after 3 months.

We did not observe an increased risk of infection in patients with central venous catheters. In our retrospective cohort, three different plasma replacement solutions were

used: albumin, FFP and albumin + FFP. Given the low numbers in each group, no comparison in terms of efficacy of the replacement fluids could be made.

Study Limitations

Our study has several limitations, including the retrospective design, lack of a control group, heterogeneous patient population, and the low number of patients, making subgroup analysis impossible.

Conclusion

In conclusion, PLEX might still be an option as an adjunct therapy, especially in a subgroup of AAV patients, of whom the characteristics need to be defined in well-designed RCTs with a larger number of patients.

Ethics

Ethics Committee Approval: This study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethical Committee for Clinical Studies (date: 02.06.2022, approval number: 396452).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.E., A.E.E., M.C.A., Concept: S.U., E.S., M.M., İ.F., Design: G.H., V.H., Data Collection or Processing: Y.Ö., T.A., Analysis or Interpretation: Y.Ö., S.N.E., Literature Search: Y.Ö., T.A., S.N.E., Writing: Y.Ö., T.A., S.N.E., G.H., M.C.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

References

1. Walsh M, Collister D, Zeng L, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ 2022;376:e064604.
2. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. Trials 2013;14:73.
3. Hughes GR. Plasma exchange (plasmapheresis). Agents Actions Suppl 1980;7:62-5.
4. McKenzie PE, Taylor AE, Woodroffe AJ, Seymour AE, Chan YL, Clarkson AR. Plasmapheresis in glomerulonephritis. Clin Nephrol 1979;12:97-108.
5. Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis 2010;69:1036-43.
6. Pepper RJ, Chanouzas D, Tarzi R, et al. Intravenous cyclophosphamide and plasmapheresis in dialysis-dependent ANCA-associated vasculitis. Clin J Am Soc Nephrol 2013;8:219-24.
7. Harper L, Savage CO. ANCA-associated renal vasculitis at the end of the twentieth century--a disease of older patients. Rheumatology (Oxford) 2005;44:495-501.
8. Zhang Y, Huang HJ, Chen WB, Liu G, Liu F, Su YY. Clinical efficacy of plasma exchange in patients with autoimmune encephalitis. Ann Clin Transl Neurol 2021;8:763-73.
9. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 1991;325:393-7.