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The Role of Therapeutic Plasma Exchange in Managing Severe ANCA-Associated Vasculitis: Impact on Renal Outcomes and Mortality

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Abstract
Plasma exchange, a treatment for antineutrophil antibody (ANCA)-associated vasculitis, has been used since the early 1940s. It involves extracting and storing blood in a refrigerator for a week, reducing antibody levels and serum creatinine levels. The procedure was first used in the 1970s to improve transplant life and still in 2024 to treat Goodpasture's disease. Plasma exchange can be carried out using centrifugation or filtration, with modern systems maintaining continuous control over the interface. While no evidence supports plasma exchange in treating vasculitis-associated pulmonary bleeding, numerous non-randomized studies have advocated for its use as a standard metric. The medication is productive in managing ANCA-associated vasculitis, resulting in profound renal failure and reduced dependence on dialysis. The establishment of an extensive organized trial network in Europe, the USA, Canada, and Australia has played a significant role in the advancement of top-notch, researcher-led, collaborative trials such as PEXIVAS.
Keywords: *antineutrophil antibody (ANCA), vasculitis, Goodpasture's disease, Plasma exchange, renal failure*

Introduction

This article aims to offer a concise overview of the existing data about the use of plasma exchange in the treatment of ANCA-associated vasculitis. Neither this study nor the relevant studies address the impaired immune system or additional possible causes of vasculitis. The data is summarized after a concise overview of the evolution of the exchange of plasma and its various uses. This overview includes nonrandomized data relevant to patients experiencing pulmonary bleeding, randomized controlled studies, two systematic reviews, and the current enrollment of participants for the PEXIVAS research. The objective of this article is not to encompass all the information about the issue but rather to offer the reader a concise overview of the history and the latest relevant data regarding the topic.

Literature Review

Plasma exchange was first demonstrated in research conducted on animals in the early 1940s [1]. Following the process of centrifugation, the blood obtained from the left ventricular heart of the

rabbit was separated into plasma and other components. The decision was made to resuspend and reinsert red blood cells. The operation was carried out on a daily basis until a total of up to 200 milliliters of plasma had been extracted. A description of a regular plasma exchange in humans was made in the year 1952 [2]. In order to accomplish this, 500 milliliters of blood were extracted and were then stored in a refrigerator for one week. Red cells that had been retrieved were then reinfused into the patient after the serum had been withdrawn. The procedure consisted of drawing blood with a single needle, which was then followed by the reinfusion of the red cells that had been taken the previous week. The operation had been performed on two patients, each of whom had been undergoing it for some time greater than one year. In the year 1960, Smolens et al. described the process of treating a patient who had Waldenstrom's macroglobulinemia [3]. This indicated that the approach had received some degree of simplification. After the removal of blood, the cells were centrifuged, mixed with acid–citrate–dextrose, and then reintroduced to the patient within two and a half hours. The procedure was carried out on one patient for fifty-one days, during which time 62 units of blood and 18 liters of plasma were extracted. The patient showed some signs of clinical improvement.

In the 1970s, it was suggested that plasma exchange may be utilized to enhance the longevity of a transplant [4]. This would result in an increase in the lifetime of a pig-to-dog xenograft from ten minutes to one hundred minutes. According to a report that was published by Lockwood in 1975, the treatment of Goodpasture's disease included the utilization of plasma exchange in addition to immunosuppression. It was noted that he had a decline in the levels of anti-glomerular-basement-membrane (GBM) antibodies, which was subsequently followed by a decrease in the levels of serum creatinine (SCr) [5]. Subsequently, four examples from Australia were documented, all of which involved a temporary restoration of kidney function, although it was only temporary for certain patients [6].

From 1977 till now 2024, the first reports of therapeutic interventions for the management of human transplant rejection were made. The findings indicated that certain patients exhibited a favorable response when plasma exchange was incorporated into various medications that are often used for managing rejection [7]. The session was carried out over a period ranging from two to eight days, and during each session, three to four liters of saline or albumin, as well as one unit of fresh-frozen plasma, were swapped.

There were a number of publications that were published between the years 2019 and 2024 that suggested new applications of plasma exchange in the treatment of a variety of disorders. Additionally, reports began to warn about the likelihood of infection as a consequence that could emerge as a result of taking such a medication [14].

Material and Method

Plasma Exchange: Plasma exchange can be performed using either centrifuge or filtering methods. The first step to be utilized is filtration, which entails the use of a membrane with relatively big holes measuring 0.2-0.7 μm in order to eliminate all plasma elements. However, dialysis membranes have pores with a size of 10 nm [15].

Filtration Process: The filter is capable of removing all giant molecules, including numerous types of immunoglobulin that have a permeability ranging from 80 to 100 percent. This will also remove any molecules that are of a lesser size. Furthermore, centrifugation is highly efficient in

eliminating all plasma; thus, there is no maximum threshold for extracting the most crucial molecule. In the past, centrifugation machines needed to be set up manually, and the position of the plasma-to-cell contact in the centrifuge had to be adjusted based on the hematocrit for every patient. This was done to ensure precise findings.

Modern systems can consistently control the interface in a system that operates continuously. This approach optimizes the efficiency of plasma clearance while concurrently minimizing cellular depletion [16]. The purpose of double-filtration plasmapheresis [17] is to restore the patient with the lower molecular weight particles that would otherwise be removed during filtration. This is achieved by decreasing the number of molecules that are lost. Alternative methods have been investigated, with the initial approach being electrodialysis. This involved passing the blood through an electric field, which attracted and removed the larger molecules with a negative charge. This was the initial method that was attempted.

Results

This study could not find any evidence to substantiate the use of plasma exchange in treating vasculitis-associated pulmonary bleeding. Several non-randomized examinations have been conducted, and a number of these research have strongly endorsed its usage as a standard measurement. This strategy often leads to challenges when it comes to achieving a balance in conducting randomized trials that have enough statistical power and are of high quality. Upon evaluating the outcomes of a cohort of twelve patients who underwent immunosuppression and plasma exchange, Aydin et al. determined that the treatment was efficacious and recommended its implementation for all patients experiencing renal failure and alveolar hemorrhage [18].
In contrast, a study conducted in 2005with Japanese patients, of which 90 percent had myeloperoxidase (MPO)-ANCA. Out of these patients, 53 received treatment with plasmapheresis [19].

Table 1: The criteria for determining which studies are included and excluded.

Title	Inclusion	Exclusion
Szpirt 2010 [31]	All patients with a new diagnosis of WG who were c-ANCA or PR3-ANCA positive from March 1990 to December 1995. Clinical manifestations as defined by Fauci and Wolff [33] 1973 from at least 2 organ systems, histology- proven WG, and positive ANCA by IIF and ELISA. All patients fulfilled the ACR 1990 classification for WG	Not stated
MEPEX 2007 [30]	Biopsy-proven ANCA-associated necrotizing GN with AKF [creatinine > 500 µmol/L (5.65 mg/dl)]. Mean age 65 years	Age <18 or > 80 years; inadequate contraception; pregnancy; previous malignancy; hepatitis B antigenemia or hepatitis C antibody or HIV infection; other multisystem autoimmune disease; circulating anti-GBM antibody or linear staining of GBM on histology; life-threatening nonrenal manifestations of vasculitis; dialysis for >2 weeks before entry; creatinine > 200 µM (2.26 mg/dl) >1 year before entry; > 2 weeks treatment with CPA or AZA; > 500 mg of MP IV; plasma exchange within the preceding year; > 3 months' treatment with prednisolone orally; allergy to study medications
Canadian Apheresis Study 1992 [28]	RPGN of undefined etiology (idiopathic or postinfectious disease) with specific pathologic criteria. Adults (16–75 years), normal-sized kidneys, SCr > 170 µmol/L and/or increasing by 44 µmol/l/week. No evidence of systemic disease or ABM antibody-induced disease. Renal biopsy within 5 days of study entry	Cellular crescents in < 50 % nonobsolescent glomeruli; evidence of serious infection or active ulcer disease
Pusey 1991 [27]	Focal necrotizing GN with crescents (WG, systemic vasculitis, polyarteritis, idiopathic RPGN)	Anti-GBM disease, SLE, HSP, chronic GN. Previously treated with MP IV, CPA or PE
Glockner 1988 [26]	RPGN with >70 % crescents on kidney biopsy. CrCl <50 ml/min. Urine output >200 ml/24 h	Anti-GBM disease, life-threatening conditions, contraindications to immunosuppression, previous treatment with AZA or CPA for >14 days
Mauri 1985 [37]	Histologically proven crescentic GN and rapidly progressive renal impairment	Less than 60 % glomerular involvement, primary glomerulopathies, transplanted kidneys, SLE, HSP
Rifle 1980 [24]	New-onset RPGN with >50 %	Goodpasture's syndrome; IgA glomerular crescents nephropathies; SLE; systemic disease

They asserted that plasma exchange was ineffective. Following a retrospective assessment of 14 and 20 patients [20, 21] determined that plasma exchange yielded positive outcomes. One of the justifications that supported the effectiveness of plasma exchange was the idea that ANCA is hazardous, which is backed by animal experimental data [22].

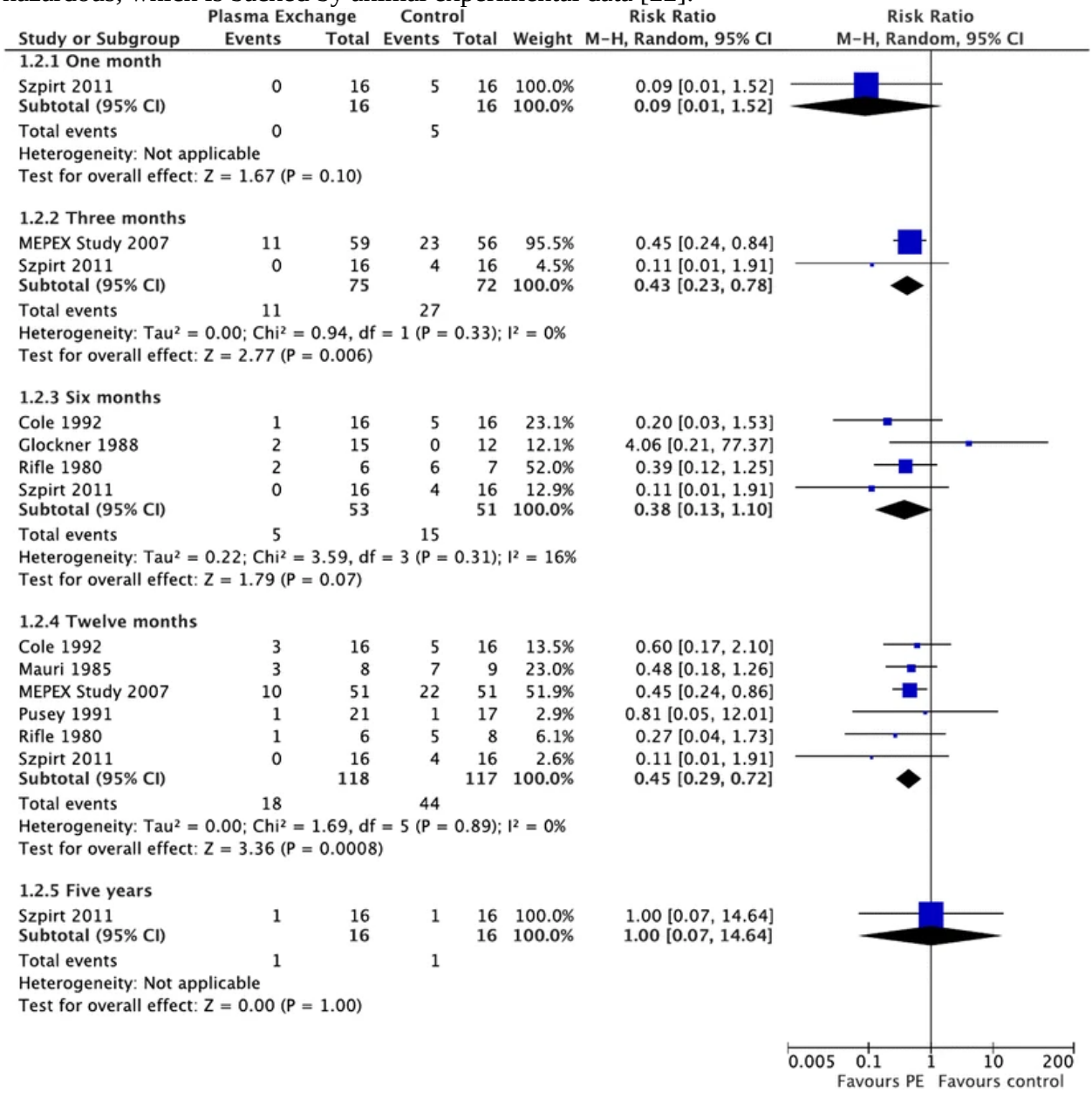

Figure 1: Impact of the exchange of plasma on the need for dialysis over time.

Plasma exchange, which removes antibodies, provided more evidence supporting the effectiveness of this procedure. Plasma exchange has been shown to be effective in treating RPGN induced by vasculitis, as supported by particular data. The pathogenesis of lung bleeding appears to be comparable to that of connected RPGN, suggesting that the same treatment may be efficacious in treating lung hemorrhage. The clinician is under significant pressure to use plasma exchange due to the lack of precise data on its benefits, as well as the retrospective statistics, the

rationale for removing ANCA from circulation, and the often severe condition of patients with pulmonary hemorrhage.

Discussion

Data on the use of plasma exchange as a therapy for pediatric vasculitis are currently lacking from randomized studies. A complete case series of 32 children who received plasma exchange treatment at the Renal Unit of Great Ormond Street Hospital in London, United Kingdom, between the years 1993 and 2003 was the subject of the most recent and comprehensive investigation. Between 1993 and 2003, the research was carried out. Twelve of these children were given treatment for vasculitis that was associated with ANCA [23]. This medication was administered to these children. The typical immunosuppressive regimens were administered to every patient, and plasma exchange was additionally performed as part of their treatment. It is not possible to draw any substantial conclusions about the effectiveness of the plasma exchange component of their treatment despite the fact that the overall results were favorable. On the other hand, the results appeared to be overwhelmingly positive.

Eight randomized controlled studies have been conducted to explore the effectiveness of plasma exchange in the treatment of renal disease that is related to pauci-immune vasculitis in patients. During the preceding three decades, there have been significant breakthroughs made in the field of clinical vasculitis research. These clinical trials give evidence to support these advancements. Varying trials had varying criteria for inclusion and exclusion, patient groups, treatment procedures, and overall research quality. These criteria varied from experiment to experiment. When it comes to the treatment procedures and processes, Tables 1 and 2 not only provide a short overview of the criteria for including and excluding participants, but they also detail the methods and processes themselves.

In a study that Rifle and his colleagues carried out, in which they investigated fourteen patients, the results of their investigation were published [24]. On the contrary, there was not a single piece of empirical evidence that could support the employment of a randomization method. The majority of the biopsies that were performed revealed the presence of antibodies or complement factors that could be detected. It should be noted, however, that the clinical manifestations of the individuals varied. There was just one patient who showed any signs of improvement out of the eight patients who did not receive treatment with plasma exchange. On the other hand, out of the six patients who were given the medication, five of them exhibited symptoms of improvement. The research does not fulfill the significant quality requirements that are being evaluated in the test that is currently being conducted.

The outcomes of a study that Mauri and colleagues carried out on a total of 22 patients who were randomly assigned to either plasma exchange or a control group were detailed in the paper. There were a number of disorders that were discovered in these people, including idiopathic RPGN and vascularitis (n = 9). According to the findings of their research, the authors concluded that patients who had an initial SCr level that was higher than 800 µmol/l (9.0 mg/dl) achieved favorable outcomes since they were treated with plasma exchange. In addition, the results of their research indicate that those who have creatinine levels that are lower than that threshold have a significant benefit.

In the year 2024, in they published their findings [26], which provided a comprehensive account of the outcomes of a trial that involved a total of 26 patients who were randomly assigned to

undergo plasma exchange. In total, twenty-six patients were being treated. All three of the patients were diagnosed with scleroderma, polyarteritisnodosa, and systemic lupus erythematosus; however, the bulk of the patients were diagnosed with idiopathic rapidly progressive glomerulonephritis (RPGN). Two patients were diagnosed with vasculitis, and one patient was diagnosed with all three disorders at the same time. After administering cyclophosphamide (CPA) for two weeks, followed by the administration of azathioprine (AZA), a minimal degree of immunosuppression was achieved. This was accomplished by administering azathioprine. It should come as no surprise that this study did not discover any evidence of varied results being obtained by the various groups.

Conclusion

Plasma exchange has been proven to be an effective treatment for ANCA-associated vasculitis, a disorder that causes severe kidney failure and reduces the need for dialysis. The current treatment does not seem to have any other significant function at this time. Plasma exchange is the preferred treatment for moderate to severe pulmonary bleeding, and it is performed based on a practical approach using past data sources. The PEXIVAS trial is expected to yield reliable evidence on the use of plasma exchange in a larger cohort of patients with milder forms of kidney failure. Furthermore, it is worth noting that this study will yield the initial randomized data on the treatment of pulmonary bleeding.

The gradual enhancement in the caliber of research and data throughout the last thirty years is a result of the establishment of progressively larger organized trial networks in Europe, the United States of America, Canada, and, more recently, Australia. These networks have been built in many nations. There is an expectation that this trend will persist as established networks expand their support base and actively pursue opportunities to form connections with new networks. This would constitute a favorable advancement. This will result in the establishment of extensive, superior, researcher-initiated, cooperative investigations like PEXIVAS, which will ultimately become the standard rather than the infrequent occurrence in the field of nephrology.

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