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Plasma Exchange in Alzheimer's Disease

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ABSTRACT

Therapeutic plasma exchange (TPE) has traditionally been used to selectively remove pathologic contents including autoantibodies, abnormal proteins, immune complexes, or toxins from a patient's plasma. In addition to the removal of molecular contributors to disease, fluid replacement and infusion of beneficial plasma constituents including albumin can be tapered based on the pathophysiologic mechanisms of the offending disease. This treatment modality has shown efficacy in symptomatic relief and slowing of disease progression for various neurologic, immunologic, and hematologic diseases. This review outlines the rationale for TPE in the treatment of Alzheimer's Disease (AD) through a potential mechanism leveraging the concentration gradient of amyloid β peptides and the infusion of albumin, and critically reviews the clinical evidence for treatment of AD using TPE and albumin replacement. This review also highlights potential sources of bias that must be considered in conjunction with the evidence of efficacy for the use of TPE in AD.

1. Introduction

Therapeutic plasma exchange (TPE) is a treatment modality wherein a patient's blood is processed by an apheresis machine extracorporeally to separate whole blood into different fractions and selectively remove plasma with replacement using plasma or colloids, such as albumin, with or without crystalloids, such as normal saline [1]. Traditionally, by removing plasma, TPE was believed to work by lowering the concentration of pathologic contents of the plasma such as autoantibodies against cell surface antigens, abnormal proteins, immune complexes, or toxins, resulting in clinical improvement or slowing of disease progression [2]. It can also be used to reinfuse beneficial plasma constituents including albumin or other compounds based on the pathophysiologic mechanisms of the indicating condition [1]. The use of TPE is currently most common in neurologic, immunologic, and hematologic diseases. [3]. Efficacy of TPE depends on the percentage of plasma removed, the distribution of pathologic compounds within the body, the rate at which the pathologic compound is produced, and the equilibrium of the pathologic compound between the plasma and other organs [1]. A newer potential indication for TPE, Alzheimer's disease (AD), has gained interest and may bring benefit to patients by an entirely different mechanism, potentially opening a new avenue for future research. In this review we aim to examine the mechanistic foundation supporting TPE in AD, and critically evaluate the limited published evidence for this new application of an already widely used medical technology.

AD is a neurodegenerative disease defined by cognitive and behavioral impairments that culminate in dementia as well as brain regional accumulation of hallmark pathologic lesions [4]. AD is currently the sixth leading cause of death in the USA and is the most common form of dementia [5]. On the global scale, in 2019 it was estimated that approximately 57.4 million people were currently living with AD and other dementias, and that in 2016 dementia caused nearly 29 million disability adjusted life years (DALYs). This figure implies dementia represented the 23rd leading global cause of DALYs in 2016, an increase from being the 41st largest cause in 1990 [6]. Models forecast sustained increases in dementia prevalence, with an anticipated 150 million cases globally in 2050 [7]. While rare autosomal dominant forms are caused by mutations in a few genes whose products are related to proteolytic processing of amyloid precursor protein (APP), the etiology of the much more common 'sporadic' AD is unknown [4]. The pathologic changes of all forms of AD are characterized by the accumulation of plaques

Abbreviations: TPE, Therapeutic plasma exchange; AD, Alzheimer's Disease; IVIG, Intravenous Immunoglobulin; ASFA, American Society for Apheresis; AChEI, Acetylcholinesterase inhibitors; Aß, Amyloid beta protein; NFT, neurofibrillary tangles; P-tau, phosphorylated tau; NMDA, N-methyl D-aspartate; BBB, Blood brain barrier; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activites of Daily Living; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-sb, Clinical Dementia Rating Sum of Boxes; ADCS-CGIC, Alzheimer's Disease cooperative study-clinical global impression of change; MMSE, mini-mental state examination.

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formed by extracellular aggregates of amyloid β (Aß) peptides, which derive from endoproteolytic cleavage of APP, as well as the presence of intracellular neurofibrillary tangles (NFT) composed of phosphorylated tau (P-tau) proteforms [8]. It is prudent to mention that there have been investigations into allegedly fabricated images featured in landmark papers supporting the association between Aß and AD, although the full implications of this discovery are still unknown [9].

The most common presenting symptom for AD is episodic short term memory loss, often followed by impaired problem-solving, judgement, executive functioning, and disorganization of thought. Mild AD dementia is characterized by cognitive impairment that is sufficiently advanced such that an individual no longer is able to perform some activities of daily living without assistance. Moderate AD dementia is characterized by development of disordered language, impairment of visuospatial skills, incontinence, sleep disturbances, and neuropsychiatric symptoms including apathy, social withdrawal, psychosis, and wandering. Severe AD dementia is characterized by dyspraxia, extrapyramidal motor signs, disorientation, difficulty communicating, and profound executive dysfunction leaving individuals dependent on caregivers [4,10,11]. The Mini-Mental State Exam (MMSE) is a widely used, validated, and reliable method of screening for AD and can be used to stratify patients into mild (score 20-26), moderate (score 10-19), or severe (score $<$10) cognitive impairment [12].

Despite a global effort, there is no cure for AD and the estimated annual cost to the USA health care system is $172 billion [4]. Current treatment for AD is symptomatic and has not been shown to slow disease-related damage and neuronal death leading to morbidity and mortality. There are only 3 drug classes with FDA approval for the treatment of AD: acetylcholinesterase inhibitors (AChEI), partial N-methyl D-aspartate (NMDA) antagonists, and recently an Aß binding antibody. It is important to note that several small molecule inhibitors, including those targeting Aß, tau, ß-secretase, and γ-secretase have for the most part failed in the clinical trial pipeline [13–15].

2. Physiologic Association Between Albumin and Alzheimer's Disease

The role of albumin replacement in TPE is being investigated as a new therapeutic approach for AD. Albumin is a potent extracellular antioxidant, contributes to endothelial stability and vascular integrity, sequesters endogenous and exogenous toxins, and exerts immunomodulatory and anti-inflammatory effects such as modulating downstream effects of the cytokines TNFα and IFN-γ [16,17]. There is an increased level of albumin oxidation in the CSF of patients with AD compared to healthy controls, suggesting the antioxidant properties of albumin may play a role in this disease [18]. Additionally, plasma albumin from patients with AD is more glycated and nitrotyrosinated compared to healthy controls, suggesting a potentially reduced ability to inhibit Aß aggregation [19]. Notably, the albumin used in TPE is oxidized to a greater extent than native albumin due to processing requirements, and the degree of albumin oxidation in the human body is significantly increased by TPE itself [20].

Preclinical studies have demonstrated a dynamic equilibrium across the blood brain barrier (BBB) between plasma Aß and CSF Aß [21]. Albumin, the most abundant protein in the plasma and CSF, binds to Aß with a high affinity and capacity, and may participate in inhibition of Aß assembly as well as favor disassembly of aggregated Aß fibrils [22]. Previous studies have demonstrated that approximately 90% of Aß in the plasma is bound to albumin, a smaller proportion is bound to lipoprotein, and very little remains freely circulating [23,24]. It has been reported that up to 40% of CSF Aß is bound to albumin [25]. A recently published trial investigating the relationship between serum albumin levels and Aß deposition measured using multimodal brain imaging in participants without dementia reported an association between low serum albumin, even within the normal range (3.5-5.5 g/dL), as a continuous variable, and increased cerebral Aß deposition in 4 regions of interest: frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal [26]. A physiologic reduction in serum albumin may reduce Aß binding capacity leading to an altered balance between CSF and serum Aß. Taken together, these results support the "peripheral sink" hypothesis, wherein removal of peripheral albumin-bound Aß from the plasma will result in Aß shifts from the CSF into the blood plasma, effectively altering the concentration gradient such that Aß will continue to sequester out of the brain and into the plasma. A visual outline for the ways albumin replacement with TPE may benefit patients with AD is displayed in Figure 1.

The dynamic relationship between Aß in brain parenchyma and in serum has been described as a complex system involving one-way receptor-mediated transport mechanisms on both sides of the BBB. However, in AD, oxidization of the Aß transporter low-density lipoprotein receptor-related protein-1 (LRP1) on the parenchymal side of capillary endothelium and the Aß transporter receptor for advanced glycation end products (RAGE) on the luminal side appear to alter the brain-CSF interface in such a way as to promote interstitial accumulation and subsequent Aß aggregation in brain [27,28]. Pre-clinical studies targeting the LRP1 pathway using recombinant LRP fragments have shown increased clearance of Aß peptides in mice hippocampus, cortex, and cerebrospinal fluid following treatment, while inhibition of the rage-ligand interaction in mice appears to suppress accumulation of Aß in brain parenchyma [29–31]. Given these alterations in Aß BBB transport mechanisms, an alternative approach involving liquorpheresis (CSF filtration) with albumin exchange has been proposed to bypass this barrier [32]. The "peripheral sink hypothesis" is further suggested by by an association with a concentration-response relationship between low serum albumin and cognitive impairment in large population-based samples of elderly adults [33,34]. Taken together, these data suggest a potential mechanism whereby a shift in the peripheral-central albumin equillibrium among patients with AD may promote Aß trapping in brain and contribute to plaque formation. Supporting this are the results of a recent retrospective clinical trial that showed a higher amount of soluble Aβ_{42} was associated with a reduced risk of AD progression among patients with AD-causing mutations. What remains to be seen is whether these preclinical data can be translated into a treatment for people with AD.

3. Clinical Evidence for TPE With Albumin in AD

The recently published primary results of the phase 2b/3 Alzheimer's Management by Albumin Replacement (AMBAR) study show that TPE with albumin exchange may slow cognitive and functional decline in patients with AD dementia [35]. The AMBAR program has, to this point, completed phase 1 (2005), phase 2 (2007), and phase 2b/3 clinical studies (2018). The phase 1 and 2 studies investigated the effects of plasma exchange with albumin infusion in patients with mild to moderate AD. The phase 1 trial included 7 patients who underwent TPE with albumin replacement twice a week for 3 weeks [36]. At the conclusion of their 1 year follow-up period, no significant changes were found in MMSE or AD assessment scale-cognitive subscale (ADAS-Cog); however, imaging suggested increased volume in the hippocampus and increased perfusion in the frontal and temporal cortices. CSF Aβ_{40} and Aβ_{42} concentrations decreased after each plasma exchange and returned to baseline prior the next procedure, a phenomenon described as a "sawtooth" pattern. Based on the feasibililty demon-

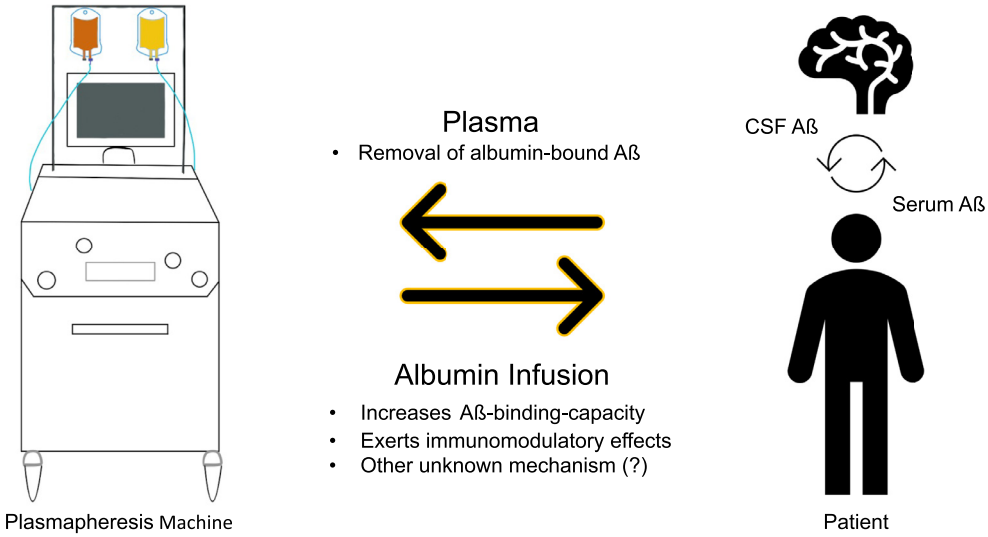

Fig. 1. Schema for Albumin Replacement with TPE in AD. The mechanism by which albumin infusion with TPE may benefit patients with AD remains unclear, although evidence supports that an increase in Aß-binding capacity and immunomodulatory effect may be involved.

strated in the phase 1 trial, a phase 2 trial was conducted involving 19 patients with mild-to-moderate AD in the intervention group and 20 sham-treated patients [37]. Those randomized to the intervention underwent TPE with albumin replacement twice a week for 3 weeks, then weekly for 6 weeks, then once every 2 weeks for 12 weeks. At 6 months, there was a nonsignificant trend towards improved MMSE and ADAS-Cog among the treatment group compared to control. Results once again demonstrated the sawtooth pattern in CSF Aß concentrations, and showed a trend towards an increased (improved) CSF $Aß_{42}$ but not $Aß_{40}$ concentration in the treatment group compared to the control group after the last plasma exchange. Additionally, results of a neuroimaging analysis demonstrated expected reduction in brain volume and impairment of perfusion in the placebo group, but stable brain perfusion in the intervention group [38].

Beginning in 2011 and randomizing a total of 347 patients at 41 sites in Spain and the United States, AMBAR was a phase 2b/3 double-blind, placebo-controlled randomized controlled trial [35]. Patients with mild-to-moderate AD dementia (MMSE 18-26) were randomized in a 1:1:1:1 ratio to a placebo arm, a low albumin group (20g albumin), a low albumin with IVIG group (20g albumin alternated with 10g IVIG 5%), and a high albumin with IVIG group (40g albumin alternated with 20g IVIG 5%). The control (placebo) group underwent a simulated TPE treatment through a noninvasive procedure (sham). The placebo protocol used a conventional TPE device loaded with fluid mimicking plasma that was connected to a cut catheter stitched to an adhesive patch and placed over the subclavicular or jugular region that circulated in a closed-loop circuit but without any actual fluid interchange between the device and subject. All participants underwent a 6-week period of weekly high-volume TPE, removing 2500 to 3000 mL of plasma with replacement 5% albumin, followed by a 12-month period with monthly lower-volume (650-880 mL) plasma exchange treatment sessions based on their randomization. Enrollment criteria included currently being treated with AChEI and/or NMDA with the previous 3 months at a stable dose. The coprimary outcomes were the change from baseline to the end of the treatment period in AD Cooperative Study-Activities of Daily Living (ADCS-ADL) and ADAS-Cog. Secondary outcomes included changes in scores of cognitive, functional, behavioral, and overall progression tests, as well as changes from baseline in CSF and plasma Aß peptide and tau concentrations.

Table 1
Potential advantages and disadvantages of plasmapheresis in alzheimer's disease.

Potential advantages	Potential disadvantages
Mechanistic evidence of peripheral sink: Albumin binds amyloid-beta	Central line dependency
Antioxidant properties of albumin	Rigorous treatment schedule
Lack of alternative treatment options	Limited evidence of efficacy
Supportive evidence from the AMBAR trial	Unclear impact on quality of life

At 14 months, participants in the TPE-treated group vs the placebo group experienced significantly less decline in ADCS-ADL (52%; $P = .03$), Clinical Dementia Rating Sum of Boxes (CDR-sb) (71%; $P = .002$), and ADCS-clinical global impression of change (CGIC) (100%; $P < 0001$), as well as a non-significant increase in ADAS-Cog (66%; $P = .06$). Differences in ADAS-cog and ADCS-ADL scores were unchanged in those participants with mild AD. Differences in treatment effect on ADCS-ADL and ADAS-Cog were insignificant between the 3 TPE-treated groups. These changes aligned with the improved clinical outcomes seen in moderate AD patients.

Importantly, there was a statistically significant improvement in quality of life (QoL) measured by a self-reported questionnaire among patients with mild-AD from baseline to 14 months among the TPE-treated groups compared with the control group. A self-reported improvement was not seen among patients with moderate-AD, although an improvement in QoL was reported by caregivers among this population, perhaps suggesting diminished awareness of cognitive and functional impairments in the moderate-AD group [39]. While all patients enrolled in the AMBAR study were receiving AChEI and/or NMDA antagonists at enrollment and throughout, the placebo group received sham TPE and thus does not represent the same QoL as those being treated with these medications alone in the outpatient setting.

In biomarker analyses, no significant change was observed in CSF $Aß_{42}$ concentration in all moderate AD TPE-treated groups, whereas in the placebo group a significant decrease and increase

were observed in CSF Aß$_{42}$ and tau proteins, respectively. A total of 297 patients provided CSF samples at baseline. Baseline CSF-Aß$_{42}$ concentration remained stable in the TPE-treated groups while it decreased (pathologic direction) in patients with moderate AD in the placebo groups at both the 2 and 14 month timepoints. This may be a result of TPE increasing clearance of Aß$_{42}$ from the central nervous system, while the decrease in CSF Aß$_{42}$ concentration only in the placebo group may be interpreted as increased Aß$_{42}$ deposition in brain. Among mild AD patients, trends in CSF biomarkers for amyloid and tau were "inconclusive or even counterintuitive" according to the authors. The lack of clear evidence of a disease-modifying pattern in CSF biomarkers suggest alternative mechanisms to amyloid clearance including albumin oxidation or immunomodulatory effects. Future studies investigating the mechanism by which albumin replacement may impact AD pathogenesis should measure baseline and interval changes in plasma and matched CSF biomarker concentrations.

Safety analysis within the AMBAR study showed 10.6% of TPE procedures were affiliated with at least one adverse event (AE). A total of 814 (47.4%) initial TPE procedures were performed through peripheral access, with the remaining performed through a central line. The decision to perform the plasma exchange through a peripheral or central vein was made on an individual basis according to "the individual characteristics of the patient" [35]. Procedures performed through central line were associated with a higher rate of AE (20.1%). Among the TPE arms, the most common adverse events were local catheter reactions, ranging between 3.0 and 3.5% between study arms, and hypotension, ranging between 2.6 and 3.1% between study arms. The groups including IVIG appeared to be associated with more frequent and more severe AEs. The dropout rate due to AE was 1.3% (n = 1/80) in the placebo group and ranged from 7.7% (n = 6/78) to 17.4% (15/86) between treatment arms. Serious adverse events (SAEs) were more frequently observed in groups receiving low-albumin+IVIG (20.3%) or high-albumin+IVIG (22.1%) compared to the low-albumin only (10.3%) and placebo groups (10.1%). Given the noninvasive approach of the placebo group, comparable rates of SAEs between the low-albumin and placebo groups likely reflect sequelae of AD and an elderly patient population. This is further evidenced by a wide variation in organ system involvement for SAEs in both the placebo and low-albumin groups. While the adverse event profile may be expected for patients undergoing plasma exchange, the relatively high proportion (52.6%) of patients receiving transfusion through a central line for high-volume TPE may pose logistical and feasibility concerns for patients. Further studies should consider whether the initial high volume plasma exchange through a central vein is necessary.

The addition of IVIG to the protocol in the phase 2b/3 trial was based on results from previous trials that investigated albumin replacement in combination with IVIG and showed that IVIG may correct a possible immunologic deficit caused by plasma depletion [40]. The decision to not include a separate high-albumin only cohort without IVIG by the research team was possibly in order to avoid this immunologic deficit, although the study team does not specify this or mention a rationale for not including such a cohort. While IVIG contains antibodies against Aß, it is included in this protocol despite the authors aknowledgement that a randomized, placebo controlled trial has shown IVIG did not have any effect on cognition or function in patients with AD [41,42]. Whether or not IVIG is necessary in this protocol is unclear and needs to be investigated in a future study, especially given the higher rate of SAE found in the IVIG groups. Previous trials by the AMBAR program investigating albumin replacement for AD found only mild improvement, and the significant increase in clinical benefit observed by this most recent trial raises questions over what aspect of the protocol, or simply sample size, made the difference.

4. Possible Bias

Given the slow pace of the novel treatment pipeline for AD, it is appropriate to be skeptical that TPE, a modality that has been around for over 100 years, might be a substantial breakthrough in treatment [43]. We aknowledge several sources of bias within this manuscript that must be considered, most notably the reliance for evaluating the clinical efficacy of TPE in AD on a single study. A thorough literature search as well as review of ongoing clinical trials was conducted and to date, the AMBAR trial represents the only clinical trial we could identify exploring the effects of TPE with albumin exchange in AD. We believe it may be worthwhile to explore more evidence and perform more trials to examine the effects of TPE in AD.

The AMBAR program is sponsored by a multinational pharmaceutical and chemical manufacturing company and one of the largest worldwide producer of blood plasma-based products [44]. The Bioscience Division of this sponsor remains the company's main growth driver (79.5% of net revenues in 2020), with over 10 years of quarterly sales growth driven by a recent upturn in immunoglobulin sales in the United States and Canada, and by albumin in the United States and China [45]. Particularly given the context that IVIG and human albumin supplies are limited in several countries, this remains a significant point of concern that needs to be considered when interpretating this study [46,47]. Future independent studies are prudent in order to remove this source of bias.

5. Summary/Future Directions

The recent AMBAR trial demonstrated a significant improvement in proxy measurements of AD disability among those with moderate cognitive and behavioral impairments from AD but failed to demonstrate improvement in those with mild impairments from AD, raising further questions about mechanism of action in slowing progression of moderate disease only. Additionally, we do not see a treatment difference between the 3 TPE-treatment cohorts, raising questions as to which protocol is most effective and whether the inclusion of IVIG is warranted. Table 1 summarizes potential advantages and risks of TPE in AD. Future research should be focused at elucidating the mechanism by which TPE appears to improve moderate AD symptoms. Concerns regarding quality of life and increased frequency of adverse events are present when evaluating the AMBAR trial treatment regimen. Although we see an improvement in self-reported QoL among those with mild-AD in TPE-groups compared to the placebo group, this is not the cohort that we see a treatment-related cognitive benefit in. While the results of the AMBAR trial suggest the need for continued research, the requirements on the patient and their caregivers to organize and attend weekly transfusion procedures for 6 weeks followed by monthly treatment for years, and potentially indefinitely, remains an issue that needs to be thoughtfully evaluated in future stud-

Table 2
Key end points for further research.

Measure serial serum and matched CSF biomarkers in response to TPE with albumin replacement
Compare clinical outcomes following TPE through peripheral line vs central line
Evaluate alternative treatment schedules with more and fewer transfusions
Continue longitudinal follow-up of original cohort to determine duration of treatment response and need for ongoing TPE
Measure clinical outcomes in cohort receiving high albumin replacement without IVIG
Determine the role of the antioxidant benefit of albumin, including to evaluate whether albumin modulates SLRP1 oxidation and alter flux of amyloid-beta across BBB
Measure QoL in TPE-treated groups compared to AChI or NMDA antagonists alone

ies. Although albumin is for the most part inert, the adverse event profile of frequent transfusions with IVIG, especially when involving a central line, are significantly more than those associated with oral NMDA antagonists and AChEI and likewise need to be carefully considered. Consideration for TPE for AD in future editions of The American Society of Apheresis (ASFA) Guidelines on the Use of Therapeutic Apheresis in Clinical Practice will likely depend on the results of future studies. Table 2 summarizes suggested key end points for further research investigating the efficacy of TPE in AD. Unfortunately, the grave state of the field of AD treatment is such that there are no effective treatments beyond the previously mentioned standard of care oral agents. As it stands, the evidence supporting the use of TPE in AD is very limited; and needs further research. Any treatment benefit, if present, would need to outweigh the adverse effects and impact on QoL.

Conflicts of Interest

The authors have no conflict of interest to disclose in relation to the submitted review.

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Further reading

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