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Emerging insights into the role of albumin with plasma exchange in Alzheimer's disease management

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative process that inexorably leads to progressive deterioration of cognition function and, ultimately, death. Central pathophysiologic features of AD include the accumulation of extracellular plaques comprised of amyloid-β peptide (Aβ) and the presence of intraneuronal neurofibrillary tangles. However, a large body of evidence suggests that oxidative stress and inflammation are major contributors to the pathogenesis and progression of AD. To date, available pharmacologic treatments are only symptomatic. Clinical trials focused on amyloid and non-amyloid-targeted treatments with small molecule pharmacotherapy and immunotherapies have accumulated a long list of failures. Considering that around 90 % of the circulating Aβ is bound to albumin, and that a dynamic equilibrium exists between peripheral and central Aβ, plasma exchange with albumin replacement has emerged as a new approach in a multitargeted AD therapeutic strategy (AMBAR Program). In plasma exchange, a patient's plasma is removed by plasmapheresis to eliminate toxic endogenous substances, including Aβ and functionally impaired albumin. The fluid replacement used is therapeutic albumin, which acts not only as a plasma volume expander but also has numerous pleiotropic functions (e.g., circulating Aβ- binding capacity, transporter, detoxifier, antioxidant) that are clinically relevant for the treatment of AD. Positive results from the AMBAR Program (phase 1, 2, an 2b/3 trials), i.e., slower decline or stabilization of disease symptoms in the most relevant clinical efficacy and safety endpoints, offer a glimmer of hope to both AD patients and caregivers.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative process associated with a continuum of illness that is initially asymptomatic but inexorably leads to Alzheimer's dementia, which involves progressive deterioration of cognitive function (i.e., memory, language, executive and visuospatial function, personality, and behavior) and the ability to perform basic activities of daily living [1].

The natural history of AD is idiosyncratic, but progression generally occurs over a period of decades [2–5]. From the asymptomatic onset of structural changes AD progresses to mild cognitive impairment and mostly independent function and then to an often longer period of moderate impairment that may involve gradual but marked behavioral changes (e.g., mood, anxiety, or motivation) [5,6]. As the structural deterioration progresses and dementia advances through mild, moderate and severe stages, assistance is more commonly required with basic daily activities; verbal communication can be limited; and patients may become bedridden, dysphagic, and highly vulnerable to secondary conditions (e.g., blood clots, skin infections, sepsis) [5,6]. Ultimately, for most patients, AD is the primary cause of death. The prevalence of AD in Europe is estimated around 5% (3.3 % in men, 7.1 % in women), and increases with age [7]. In the US, its high prevalence (10 % of people aged 65 and older) has made AD the sixth most common cause of death overall and fifth most common cause of death in individuals 65 years and older [8].

The central pathophysiologic features of AD include the accumulation of extracellular plaques comprised of amyloid-β peptide (Aβ), and the presence of intraneuronal neurofibrillary tangles and dystrophic neurites containing filaments of phosphorylated tau protein [9–12]. The persistent presence of neurotoxic Aβ plaques and tau neurofibrillary tangles also produces an inflammatory response in the brain [13]. A large body of evidence suggests that oxidative stress (when reactive oxygen species production exceeds cellular antioxidant defenses) is a major contributor to the Aβ clearance abnormalities underlying the pathogenesis and progression of AD [14] and may be the earliest pathogenic event in the disease [15]. Although both the presence of

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extracellular plaques and intraneuronal neurofibrillary tangles are suspected to be responsible for cell death in the AD brain, the initial biological trigger of the pathology has not been fully elucidated.

According to the amyloid cascade hypothesis [16], the inherited dominant forms of AD due to missense mutations in the APP or presenilin-1 or -2 genes result in a relative increase in production of Aβ peptides throughout life, such as $A\beta_{40}$ and the longer, more hydrophobic and self-aggregating $A\beta_{42}$. In the non-dominant forms of AD, including sporadic AD, there is a failure of Aβ clearance mechanisms that results in gradually rising $A\beta_{42}$ levels in the brain. Ultimately, in both situations a gradual deposition of $A\beta_{42}$ occurs as diffuse plaques. This triggers the formation of tau-containing tangles/neurites [17–19], which gradually spread to adjacent neurons via microtubule transport [20] and precipitate neuronal death [21]. By contrast, the tau hypothesis postulates that tau tangle pathology precedes Aβ plaque formation. This is based on the fact that intraneuronal neurofibrillary tangles have been observed in the brain of patients in an early stage of AD with no Aβ plaques [22]. However, a multifaceted approach to AD pathology that includes the interaction of both Aβ plaques and tau aggregation in parallel is a plausible scenario [23].

Another major line of research [24,25] indicates that AD-associated brain damage is less a result of Aβ plaques than of soluble, ligand-like Aβ oligomers. These are potent neurotoxins that have been shown to accumulate in brain tissue and cerebrospinal fluid (CSF). These oligomers also instigate cardinal features of AD, including tau pathology, synapse deterioration and loss, inflammation, and oxidative damage, that negatively correlate with cognitive assessment scores (e.g., on the Mini-mental State Examination [MMSE]) [25]. Interestingly, soluble oligomers (AβOs) form more readily from $A\beta_{42}$ than from $A\beta_{40}$ [26], and the C-terminus of $A\beta_{42}$ is critical for oligomer formation [27].

2. Current pharmacologic and nonpharmacologic approaches for AD

Currently, AD patients are essentially treated symptomatically. Symptomatic treatments include cholinesterase inhibitors (e.g., rivastigmine, galantamine, donepezil, tacrine) which can be used at any stage of illness, and N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., memantine), or a combination of memantine and donepezil for moderate-to-severe disease [28–30]. However, the regulatory agency of China has recently approved sodium oligomannate (GV-971), a new drug that suppressed gut dysbiosis and the associated phenylalanine/isoleucine accumulation, suppressed neuroinflammation and reversed the cognition impairment in mild-to-moderate AD patients [31].

Adjunctive therapy for AD using nonpharmacologic approaches (e.g., activity programs, music therapy, bright light therapy, aromatherapy, touch therapy [32]) may also be employed. Regimens involving these medications and modalities are used to temporarily maintain or improve cognitive and physical function and overall quality of life and reduce behavioral symptoms (e.g., depression, apathy, wandering, sleep disturbances, agitation, and aggression), but they have no effect on the underlying neuropathology, disease progression, or life expectancy [33–35].

Several molecular targets in the amyloidogenic pathway were aimed at preventing the accumulation of amyloid deposits or at reducing existing plaques for the treatment of AD [5,6,8–11]. However, with the failure of multiple clinical trials involving Aβ-targeted therapies [36–41], many researchers have come to believe that the challenge of AD is multifactorial. The pleiomorphism of the disease state, the wide variety of risk factors and precipitants (e.g., age, genetics, environmental factors, concomitant illness), and the abundance of potential drug targets can only be successfully addressed with a multitargeted approach [16,42]. Interestingly, a recent re-analysis of a phase 3 aducanumab study (the drug was initially declared ineffective after futility analyses [43]) showed that the product reduced clinical decline in a larger dataset of patients with early AD [44]. Since aducanumab is a human monoclonal antibody designed to bind and eliminate the Aβ in the brain, the amyloid hypothesis is regaining attention [45].

A therapeutic approach undergoing intensive research posits the existence of a somatic pool of Aβ that exists in dynamic equilibrium between peripheral and central sources and clearance [46]. It is suggested that facilitating peripheral Aβ clearance can induce commensurate reductions in central Aβ levels [47], thereby removing centrally aggregated Aβ and arresting disease progression. An intervention that takes advantage of this therapeutic approach is based on performing plasma exchange with albumin replacement to induce a shift in the dynamic equilibrium between brain and plasma Aβ [48]. The rationale and therapeutic potential of plasma exchange in patients with AD using albumin as the replacement fluid are summarized below.

3. Plasma exchange with albumin replacement: a new approach in a multitargeted AD therapeutic strategy

Albumin is a non-glycosylated, heart-shaped protein lacking prosthetic groups, glycans, or lipids, with a molecular mass of approximately 66 kDa (Fig. 1). It is a highly soluble, monomeric, multidomain macromolecule consisting of a single-chain polypeptide of 585 amino acid residues. Albumin is approximately 67 % α-helix with no β-sheet [49–51]. Albumin is synthesized at a rate of 9−12 g/day in polysomes bound to the endoplasmic reticulum of hepatocytes (as preproalbumin). Albumin is not stored hepatically but is secreted into the portal circulation and translocated to the extracellular space [52,53].

Albumin is the most abundant protein in plasma (50–60 % of total plasma proteins), and is also the predominant protein within bronchoalveolar lavage fluid (which is representative of components in alveolar space), CSF, and synovial fluid [54–56]. Biochemical effects of albumin are pleiotropic, a fact that compels the reframing of the relevance of albumin to numerous physiologic functions. This reframing has an impact on the clinical roles of albumin, both current and emerging.

3.1. Physiologic role of albumin

Albumin has numerous functions in the body (Table 1). Albumin is the major determinant of plasma oncotic pressure, the primary regulator of tissue fluid distribution between body compartments, and an important contributor to plasma pH [50,52,57–59]. It also serves as a key transport protein by binding naturally occurring, therapeutic, and toxic substances (Fig. 1). Significantly, albumin can bind various endogenous molecules, including long-chain fatty acids (albumin is the main fatty acid transporter), steroids, and L-tryptophan, [52,60,61] and is also involved in transporting ions in the circulation, including copper, zinc, and calcium [61]. Additionally, albumin binds exogenous compounds including drugs, such as warfarin, ibuprofen, chlorpromazine and naproxen, with their binding affinity significantly affecting their activity and half-life [52,60,61]. Furthermore, albumin also acts as a toxic waste carrier, binding bilirubin, the product of heme breakdown, to deliver it to the liver for hepatic excretion [61]. Concerning Aβ, albumin is able to bind Aβ under physiological conditions [62,63] and may play a key role in preventing the formation of Aβ aggregates, not only in plasma but also in CSF [63–66].

Importantly, albumin is the main extracellular antioxidant [67]. Albumin is an avid scavenger for different oxidative and nitrosative reactive species. Albumin's antioxidant capacity mainly relies on its Cys34 residue that can be transformed into more oxidized forms, preventing the oxidation of other entities [68]. According to the oxidation status of the thiol group (-SH) on the Cys34 residue, three forms of albumin with decreasing antioxidant capacity can be distinguished: reduced (human mercaptoalbumin; HMA), reversibly oxidized (human nonmercaptalbumin 1; HNA1) and irreversibly oxidized (human nonmercaptalbumin 2; HNA2) [69]. In addition to this scavenger activity, the metal-binding properties of albumin also contribute to its antioxidant activity [52,61]. Though its N-terminal, albumin restricts oxidative

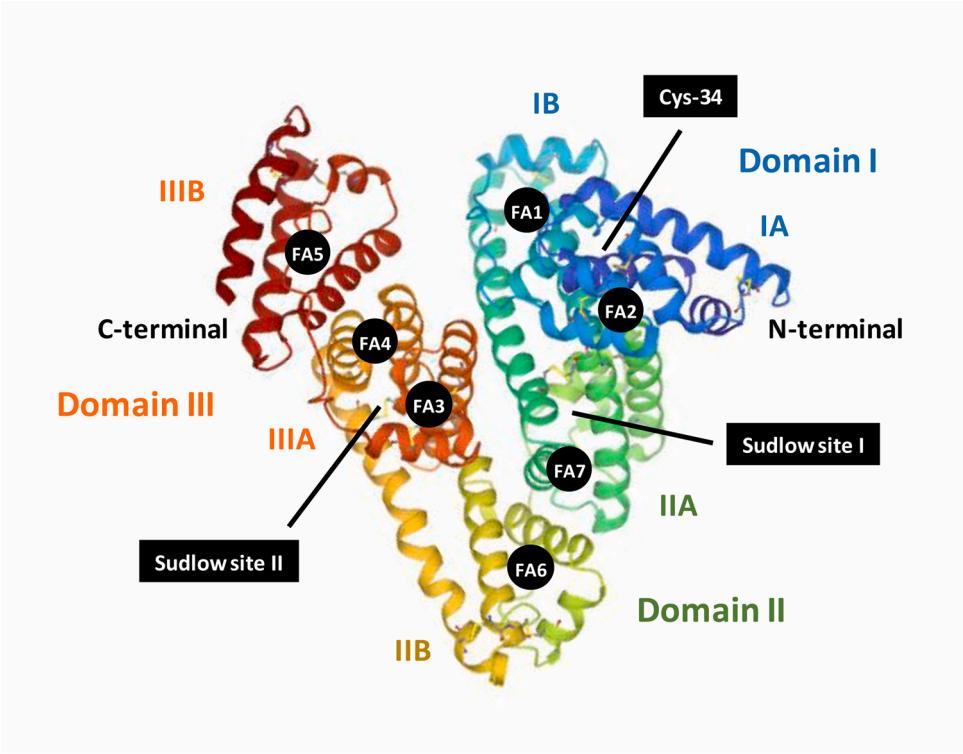

Fig. 1. Human serum albumin molecule showing the three homologous domains and subdomains, and main binding sites: fatty acid (FA) 1 to 7, cys34 and Sudlow sites I and II. Source: adapted from Protein Data Bank (PDB) ID 1AO6. 1998. DOI: 10.2210/pdb1ao6/pdb.

Table 1
Functions of albumin in the body [50,52,57–79].

- ☐ Determinant of plasma oncotic pressure
- ☐ Regulation of tissue fluid distribution between body compartments
- ☐ Contribution to plasma pH
- ☐ Binding and transport of naturally occurring, therapeutic, and toxic materials
  - ○ Long-chain fatty acids
  - ○ Steroids
  - ○ L-tryptophan
  - ○ Ions in the circulation (e.g., Cu, Zn, Ca)
  - ○ Drugs (e.g., warfarin, ibuprofen, chlorpromazine, naproxen)
  - ○ Bilirubin
  - ○ β-amyloid peptide
- ☐ Scavenging oxidative and nitrosative reactive species
- ☐ Stabilization of endothelium, vascular integrity and capillary permeability
- ☐ Hemostasis regulation (e.g., vasodilation, platelet aggregation inhibition)
- ☐ Immunomodulation
- ☐ Anti-inflammatory activity

stress damage by neutralizing ions that catalyze reactions in which free radicals are released (e.g., free Cu and Fe) [53,70,71].

Other important attributes of albumin include its role in capillary permeability, hemostasis, immunomodulation, anti-inflammatory activity, and endothelial stabilization. More than 50 % of total body albumin is present in the extravascular compartment and may directly influence vascular integrity and permeability by way of interactions with the extracellular matrix [72].

Regarding hemostatic effects, albumin can bind nitric oxide (NO) in position Cys-34. Potential clinical effects of nitroalbumin (HSA-NO) include vasodilatation and inhibition of platelet aggregation. Clinical studies have suggested that hypoalbuminemia is linked to hyper-aggregation of platelets and that albumin modifications can impact platelet aggregation [73]. This action may be modulated through nitrosoalbumin.

The mechanisms of immunomodulatory and anti-inflammatory properties of albumin are: the capacity to bind bacterial products such as lipopolysaccharides, lipoteichoic acid and peptidoglycan [74]; modulation of functions of antigen presenting cells (APCs) such as activation of major histocompatibility complexes II (MHC II) [75]; and modulation of cytokine synthesis, including interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) [75,76]. Recent insights into the intracellular signaling pathways involved in the immunomodulatory properties of albumin have shown that albumin was internalized in immune cells such as leukocytes. Albumin modulated the excessive production of cytokines through interaction with endosomal Toll-like receptor (TLR) signaling without compromising leukocyte defensive mechanisms against pathogens, such as phagocytosis [77].

The ability of albumin to modulate inflammation, reduce oxidative damage, and interfere in neutrophil adhesion could therefore potentially impact endothelial function. Beneficial effects of albumin in stabilizing the endothelium have been reported [78,79].

3.2. *Current clinical roles of albumin*

The first therapeutic use of albumin from human plasma occurred nearly 80 years ago in a 20-year old patient with traumatic shock [80]. Since then, albumin has remained valuable in a variety of clinical applications (Table 2) including hemorrhagic hypovolemia, burns, gastrointestinal and other internal bleeding, prevention of central volume depletion after paracentesis, cardiopulmonary bypass, and hypoalbuminemia (including therapeutic plasmapheresis) [81–84].

In patients with liver disease, the role of albumin was once thought to be limited to the maintenance of oncotic pressure, but albumin appears to have a range of other important functions in this patient population. In particular, multiple toxic substances (e.g., bilirubin, endotoxin, and cytokines) are albumin-bound and known to accumulate in patients with liver disease [85]. At the same time, liver impairment reduces not only albumin concentration but also leads to a qualitative and quantitative reduction in albumin function. Clinically, the severity of albumin dysfunction correlates with disease progression and the extent of hepatic compromise [86–88].

Table 2
Evidence-based use of albumin 5% and/or 25 % in clinical settings [80–94].

Clinical use	Notes
Hypovolemia	For restoration and maintenance of circulating blood volume where hypovolemia is demonstrated, and colloid use is appropriate.
Hypoalbuminemia	For patients with hypoalbuminemia who are critically ill and/or actively bleeding. Acute liver failure is a special situation in which both hypovolemia and hypoalbuminemia can be present.
Cardiopulmonary bypass procedures	Preoperative dilution of blood in cardiopulmonary bypass procedures. Albumin also may be used in the priming fluid
Plasma exchange	As a replacement fluid during therapeutic plasma exchange treatments
Acute nephrosis	To treat peripheral edema in patients with acute nephrosis who are refractory to cyclophosphamide, corticosteroid therapy or diuretics
Ovarian hyperstimulation syndrome	Plasma volume expander in fluid management relating to severe forms of ovarian hyperstimulation syndrome
Neonatal hyperbilirubinemia	Prior to or during an exchange procedure in an attempt to bind free bilirubin and enhance its excretion
Adult respiratory distress syndrome (ARDS)	In conjunction with diuretics to correct fluid overload and hypoproteinemia associated with ARDS
Prevention of central volume depletion after paracentesis due to cirrhotic ascites	To maintain cardiovascular function following removal of large volumes of ascitic fluid after paracentesis due to cirrhotic ascites

The evidence linking hypoalbuminemia and albumin dysfunction to issues with the transport and metabolism of toxic entities and disruptions of other systems habitually influenced by a normal albumin function (e.g., redox balance, coagulation, and inflammation) suggests that an "effective albumin concentration" may be an important component in maintaining homeostasis [85]. The concept can be demonstrated in several therapeutic situations. Patients with cirrhosis and spontaneous bacterial peritonitis have been shown to experience reductions in proinflammatory cytokines and endotoxin following albumin therapy [89]. This finding aligns with evidence showing that human albumin has the capacity to bind endotoxins [90]. In acutely decompensated cirrhotic patients with acute kidney injury, albumin infusion improves renal function by impacting renal blood flow autoregulation. This may be achieved through endothelial stabilization, and a reduction in the sympathetic tone, endotoxemia and oxidative stress [91]. Human albumin infusions have also been used to reduce circulating prostaglandin E_2 (PGE2) levels which attenuated immune suppression and reduced the risk of infection in patients with acutely decompensated cirrhosis or end-stage liver disease [92]. More recently, it has been described that long-term and short-term high-dose albumin treatment normalized serum albumin, improved circulatory dysfunction and induced immunomodulation in patients with decompensated cirrhosis [93].

Albumin treatment has also been studied in patients with severe sepsis. So far, beneficial effects of albumin infusion have been described in a post-hoc analysis of a patient subgroup with septic shock and linked to its non-oncotic properties [94].

3.3. Emerging insights on albumin in AD

Albumin is not only the most abundant protein in plasma but also in the CSF. Albumin has several characteristics of clinical relevance for the treatment of AD patients (Table 3). Among the most important, considering the neurological and clinical significance of amyloid deposits, are its affinity for binding Aβ and capacity for inhibiting Aβ fibrillization [63,65,95,96]. Furthermore, it is postulated that serum albumin may prevent amyloid entry into neurons thus promoting neuronal survival [97].

Table 3
Albumin characteristics of clinical relevance for the treatment of patients with Alzheimer's disease [62–65,95–124].

Characteristic	Mechanism
Prevents the growth of Aβ assemblies	☐ Affinity for binding Aβ peptide ☐ Inhibition of Aβ self-association and fibrillization ☐ Disassembly of Aβ aggregates ☐ Control of metal-free and metal-bound Aβ aggregation
Promotes neuronal survival	☐ Prevention of Aβ entry into neurons
Provides antioxidant and anti-inflammatory capacity	☐ Undergoing oxidation, glycation and nitrotyrosination ☐ Neutralization of ions

Additional studies with human serum albumin have shown, by means of *in vitro* and cell-based assays, that the formation of $Aβ_{40}$-albumin and $Aβ_{42}$-albumin complexes prevented the deleterious effects of these peptides on neuronal viability, synaptophysin expression, and PSD-95/synaptotagmin disarrangement, thus suggesting a protective effect of albumin [98]. Unlike neurons, albumin seems to be unable to prevent the deleterious effects of Aβ in astrocytes [99]. Studies performed in silico and *in vitro* suggest that the albumin C-terminus can impair Aβ aggregation and to promote disassembly of Aβ aggregates thus promoting neuroprotection [100].

In triple-transgenic AD mice, intracerebroventricularly-infused albumin has exhibited a range of beneficial effects [101], including reductions in $Aβ_{42}$, AβOs, total plaque area, total and hyperphosphorylated tau, and inflammation. In addition, an increase in tubulin (suggesting increased microtubule stability) and restoration of blood-brain barrier and myelin integrity were observed. Clinical effects included an improvement in cognitive tests, suggesting a nonimmune- or Aβ efflux-dependent means for treating AD [101].

There is some evidence that dyshomeostasis of metals and failure of metal transport, including copper, may contribute to AD pathogenesis [102]. Furthermore, albumin sequesters Zn(II) and Cu(II) from Aβ while maintaining albumin-Aβ interaction. Therefore, albumin can control metal-free and metal-bound Aβ aggregation and aiding the cellular transportation of Aβ via Aβ-albumin complexation [103].

Importantly, AD is associated with elevated levels of oxidative damage in brain and peripheral lymphocytes [104–106]. Some studies have described low antioxidant levels in plasma [107,108] from AD patients including plasma albumin [109,110] suggesting an association between the low plasma antioxidant level and the loss of cognitive function in AD [107–110]. Furthermore, in AD oxidative stress triggers oxidative modification of different proteins in the brain. The dysfunction of such proteins is likely related to the pathology of AD [111]. Consistently, high levels of protein oxidation markers have been observed in plasma from AD patients including albumin [111–114].

Albumin can also undergo glycation associated with normal aging [115]. Glycation-induced conformational changes can have a deleterious effect on both the binding capacity [116–118] and antioxidant capacity [119–121] of albumin. Furthermore, elevated levels of glycated albumin have also been associated with age-related conditions such as retinopathy, nephropathy, neuropathy, cardiovascular diseases and AD [118]. A study of the effects of the pathological post-translational modifications of albumin found that brain and plasma levels of glycated and nitrated albumin were significantly higher among AD patients than healthy controls [122]. Of note, these modifications (glycation and nitrotyrosination) promote changes in albumin structure and biochemical properties resulting in modified albumins that were significantly less effective in preventing Aβ aggregation than native albumin which

could be relevant to the progression of AD [122].

Recently, post-translational modifications of albumin (oxidation and glycation) have been compared in plasma and CSF samples from mild-moderate AD patients and healthy age-matched donors [123,124]. Regarding oxidation, levels of reduced albumin in the plasma and CSF of AD patients were lower than in healthy controls supporting the hypothesis that the albumin of AD patients was significantly more oxidized than albumin in healthy subjects. This was especially evident in CSF where the level of irreversibly oxidized albumin was around 7-fold higher than the healthy controls one [123].

In relation to albumin glycation, plasma albumin has been found to be more glycated in AD patients than in healthy controls [124]. Moreover, a different pattern of glycated isoforms was also observed in both plasma and CSF of AD patients in comparison to healthy controls, with a higher content of both oxidized + glycated and cysteinylated + glycated isoforms. Furthermore, when comparing albumin glycation in plasma and CSF samples obtained from the same patients, AD patients showed to have higher glycation of albumin in plasma than in CSF [124]. These data support the role of glycation and oxidative stress in AD and deserve further investigation.

3.4. Therapeutic plasma exchange in AD

In essence, therapeutic plasma exchange (Fig. 2) is a process by which plasma is removed from the body by plasmapheresis and replaced with a replacement fluid to eliminate toxic endogenous and exogenous substances (e.g., autoantibodies, alloantibodies, immune complexes, proteins, toxins). Albumin is one of the most frequently used replacement solutions [125]. Unlike hemodialysis, which is used to remove small molecules by dialysis, therapeutic plasma exchange predictably removes large molecules from the circulation. Therapeutic plasma exchange has been widely used in patients with neurologic disorders, including Guillain-Barré syndrome, myasthenia gravis, and chronic inflammatory demyelinating polyradiculoneuropathy [126] (Table 4). Although neurologic uses account for the majority of procedures [127], therapeutic plasma exchange also has an important role in patients with other autoimmune and inflammatory conditions. In their 2019 Guidelines on the Use of Therapeutic Apheresis in Clinical Practice [126], the American Society for Apheresis identified 84 diseases and medical conditions, with 157 indications, for which several apheresis techniques may be appropriate. Therapeutic plasma exchange with albumin replacement was among the most commonly recommended procedures. Interestingly, the use of therapeutic plasma exchange in Alzheimer's disease is under consideration for a new fact sheet [126].

Table 4
The use of therapeutic plasma exchange in neurologic conditions [126,127].

Condition	2019 ASFA Category / Grade recommendations
Guillain-Barré syndrome	I/1A
Chronic inflammatory demyelinating polyradiculoneuropathy	I/1B
Paraproteinemic polyneuropathies (IgG/IgA)	I/1B
Myasthenia gravis (moderate-severe)	I/1C
Myasthenia gravis (pre-thymectomy)	I/1C
Paraproteinemic polyneuropathies (IgM)	I/1C
Multiple sclerosis (acute relapses)	II/1B
Neuromyelitis optica	II/1B
Pediatric autoimmune neuropsychiatric disorders[a]	II/1B
Acute disseminated encephalomyelitis	II/2C
Lambert-Eaton myasthenic syndrome	II/2C
Phytanic acid storage disease[b]	II/2C
Alzheimer's disease	Considered for new fact sheet

[a] Associated with streptococcal infections and Sydenham's chorea.
[b] Refsum's disease.

Therapeutic plasma exchange is generally safe and well-tolerated with most complications being of mild to moderate severity and easily managed [128–131]. The possibility of extending the use of therapeutic plasma exchange with albumin replacement to a medical condition such as AD has been explored in recent years [132–136]. In AD, removal of neurotoxic compounds such as Aβ in plasma could be translated into clinical benefit.

Several observations support the development of clinical trials to test the efficacy and safety of therapeutic plasma exchange with albumin replacement in slowing the progression of AD. First, soluble oligomeric Aβ is more toxic than amyloid fibrils, has a higher presence in the brains of AD patients, and is associated with cognitive impairment [137]. Second, high levels of Aβ aggregates in the brain are associated with low levels of soluble Aβ in CSF in AD [138]. Third, albumin is the main transporter and main extracellular antioxidant in the human body [67]. Fourth, around 90 % of the circulating Aβ is bound to albumin [62]. Fifth, therapeutic albumin has Aβ-binding capacity and can prevent Aβ aggregation [96,139]. Sixth, a dynamic equilibrium exists between peripheral and central Aβ on the one hand and Aβ clearance on the other. An Aβ imbalance may be an etiologic event in the development and progression of AD [46,140].

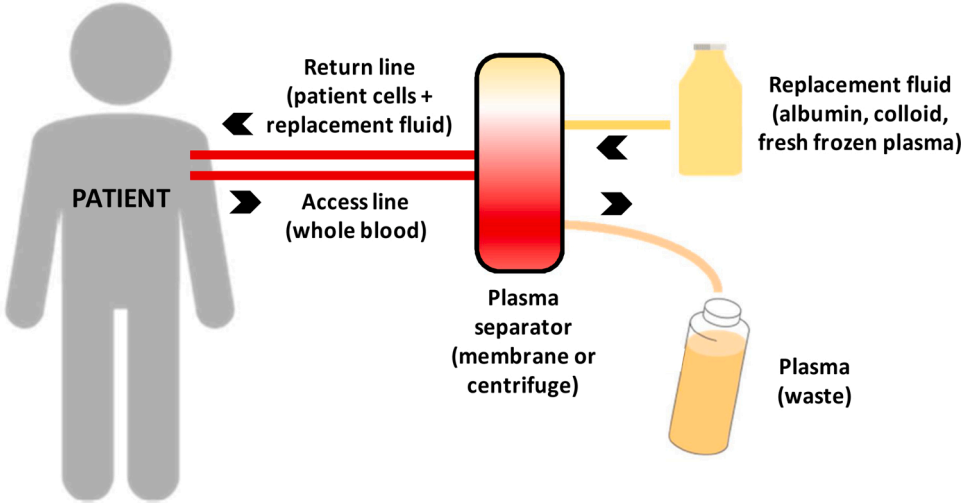

Fig. 2. A schematic drawing of therapeutic plasma exchange.

4. Clinical trials on plasma exchange with albumin replacement in AD

The Alzheimer Management By Albumin Replacement (AMBAR) clinical trial program started in 2005 with the hypothesis that plasma exchange with albumin replacement could alter the dynamic equilibrium between albumin-bound Aβ in plasma and Aβ in CSF. This was tested by replacing the endogenous albumin of patients with mild to moderate AD with therapeutic albumin (Albutein®/Human Albumin Grifols®, Barcelona, Spain) using a plasma exchange schedule [132–136]. Albutein®/Human Albumin Grifols® is purified human albumin sourced from plasma collected from relatively young, healthy plasma donors. This product retains its Aβ binding capacity and has no quantifiable levels of Aβ [139]. In addition to this effect on Aβ, based on recent investigations [122–124] plasma exchange also removes a portion of the patient's "old" and less-functional albumin (i.e. oxidized and glycated) which is replaced with "new" fresh therapeutic albumin. Remarkably, during plasma exchange not only plasma Aβ is removed but also other substances, known and unknown, including possible pro-aging systemic factors [141–144] which reinforces the AMBAR approach.

To date, the AMBAR Program has completed phase 1 (EudraCT#: 2005-001616-45), phase 2 (EudraCT#: 2007-000414-36; ClinicalTrials.gov ID: NCT00742417)and phase 2b/3 (EudraCT#: 2011-001598-25; ClinicalTrials.gov ID: NCT01561053) clinical studies, and evidence has been generated to support further investigation into the efficacy and mechanisms of the AMBAR approach. Table 5 summarizes these studies.

4.1. Phase 1/pilot study

The single-arm, open-label Phase 1/pilot study [145] established the feasibility of replacing endogenous albumin with 5% therapeutic albumin during plasma exchange as a treatment for patients with mild to moderate Alzheimer's disease. A total of seven patients with baseline MMSE scores of between 20 and 24 underwent six plasma exchanges (one plasma volume exchanged) over a period of three weeks, that is two plasma exchanges per week, with a one-year follow-up. Results showed a slight variation of plasma $A\beta_{40}$ during the plasma exchange period. For CSF $A\beta_{40}$ and $A\beta_{42}$, a decrease was observed during the plasma exchange period followed by an increase after the plasma exchange period returning to baseline levels after six months of follow-up. Cognitive assessments suggested largely stable scores on the MMSE and Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) after one-year of follow-up [145].

Table 5
Summary of clinical studies with plasma exchange and therapeutic albumin replacement (AMBAR Program).

Design	Objective	Patients	Treatment	Outcomes summary
Pilot study (proof-of-concept) [135]	☐ Assess whether PE with therapeutic albumin can mobilize CSF-plasma Aβ peptide	☐ Males and females aged 55–85 years (N = 7)	☐ Therapeutic albumin 5%	☐ Plasma Aβ varied relative to PE
	☐ Evaluate changes in cognitive status	☐ Mild to moderate AD (NINCDS-ADRDA criterion) ☐ Baseline MMSE = 20-24 ☐ Stable on donepezil ≥6 months ☐ MRI or CAT scan with no cerebral-vascular findings within 6 months	☐ 6 PE: 2 per week for 3 weeks ☐ 1-year follow up ☐ Optional study extension period (same approach)	☐ Plasma Aβ mobilization seen throughout the treatment period ☐ Patients were largely stable at 1 year
Phase 2, multicenter, randomized, patient-and rater-blind, placebo-controlled, parallel-group [132,136]	☐ Compare the mobilization of Aβ in CSF and plasma	☐ Males and females aged 55-85 years (N = 42)	☐ Therapeutic albumin 5%	☐ Decreased $A\beta_{42}$ levels in plasma and led to borderline increase of $A\beta_{42}$ levels in CSF
	☐ Evaluate changes in cognitive status	☐ Mild to moderate AD (NINCDS-ADRDA criterion) ☐ MMSE score 18−26	☐ 3 PE periods: 2 PE/weekly (3 weeks), one PE/weekly (6 weeks), and one PE/bi-weekly (12 weeks)	☐ No apparent decline in MMSE scores over 44 weeks ☐ Significant improvements on the Boston Naming Test at 20 weeks and 44 weeks and the Semantic Verbal Fluency Test at 44 weeks
	☐ Evaluate changes in neuroimaging	☐ Stable treatment with acetylcholinesterase inhibitors (≥3 months) ☐ MRI and SPECT within the 12 months of participation with no cerebrovascular findings	☐ 6-month follow-up	☐ Improvements in cognition, language, and memory sustained beyond the treatment period
Phase 2b/3, multicenter, randomized, patient and rater-blind, placebo-controlled, parallel-group [133,134,146]	☐ Evaluate changes in the cognitive, functional, behavioral and global assessment domains	☐ Males and females aged 55−85 years (N = 365)	☐ Therapeutic albumin 5% and 20 % with or without intravenous immune globulin 5%	☐ Significant reduction in disease progression at the time endpoint (14 months) in cognitive, functional and global assessment scales
	☐ Determine AD biomarker levels: $A\beta_{40}$, $A\beta_{42}$, P-tau, and T-tau in CSF, $A\beta_{40}$ and $A\beta_{42}$ in plasma	☐ Mild to moderate AD (NINCDS-ADRDA criterion) ☐ MMSE score 18−26	☐ 2 PE periods: 1 conventional PE/weekly (6 weeks), 1 low-volume PE/ monthly (12 months)	☐ Significant improvement in verbal memory, language fluency, processing speed and quality of life tests ☐ Stabilization of CSF $A\beta_{42}$ and P-tau protein levels
	☐ Evaluate changes in neuroimaging	☐ Stable treatment with acetylcholinesterase inhibitors and/or memantine (≥3 months) ☐ MRI and FDG-PET within the 12 months of participation with no cerebrovascular findings		☐ Less reduction of brain metabolism over the 14 months

AD, Alzheimer's Disease; PE, plasma exchange; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association; CSF, cerebrospinal fluid; MMSE, Mini-mental State Examination; MRI, magnetic resonance imaging; SPECT, singlephoton emission computed tomography; FDG-PET, positron emission tomography with 18F-fluorodeoxyglucose.

In an extension study using the same methodology (N = 6), levels of plasma $A\beta_{40}$ and $A\beta_{42}$ exhibited a consistent saw-tooth pattern during the plasma exchange period. These data supported the proposed mechanism of action of removal of Aβ by albumin replacement through plasma exchange. In the CSF, unlike in the pilot study, $A\beta_{40}$ and $A\beta_{42}$ levels in the CSF, tended to remain stable, as did the cognitive status of the albumin-treated patients [145]. Neuroimaging findings suggested a progressive volume increase for the hippocampus as well as a perfusion increase in the frontal and temporal areas in plasma exchange-treated patients [145].

4.2. Phase 2 study

In the multicenter, randomized, placebo-controlled, Phase 2 study (N = 42), patients treated with 5% therapeutic albumin in a plasma exchange regimen were compared with untreated (placebo, sham plasma exchange) patients [132]. Levels of $A\beta_{40}$ and $A\beta_{42}$ in CSF and plasma were determined, and cognitive, functional, and behavioral domains were assessed. Results showed that plasma exchange with albumin replacement decreased $A\beta_{42}$ levels in plasma and led to borderline increase of $A\beta_{42}$ levels in CSF. There was no significant decline in MMSE scores over 44 weeks. In addition, apheresis/albumin replacement led to statistically significant improvements in cognition, language, and memory that were sustained beyond the treatment period, suggesting that plasma exchange with albumin replacement might halt the symptom progression of AD [132]. A separate neuroimaging evaluation of structural and functional brain changes in this cohort found that plasma exchange-treated patients had less hypoperfusion ($p < 0.05$) in frontal, temporal, and parietal areas, and perfusion stabilization in Brodmann area BA38-R during the PE treatment period compared to controls [136].

4.3. Phase 2b/3 study

In the multicenter, randomized, patient and rater blinded, placebo-controlled, parallel-group Phase 2b/3 study [133,134], 347 patients with mild to moderate AD dementia were randomized (496 screened) to three active arms of plasma exchange with albumin and intravenous immunoglobulin replacement and one placebo arm (sham plasma exchange). Patients receiving active treatment underwent an initial phase consisting of weekly therapeutic plasma exchange (one plasma volume of exchange) for six weeks and replacement with albumin 5% plus a maintenance treatment phase. The maintenance phase consisted of different doses of albumin 20 % replacement for each group and monthly low volume plasma exchange sessions (removing 690–880 ml of plasma, following the scheme used in plasma donation) for a period of one year. Two of the active groups received intravenous immunoglobulin 5% every four months to replace the endogenous immunoglobulin removed by the procedure. Patients in the placebo (sham) group underwent simulated plasma exchanges.

In total, 4709 apheresis procedures were performed, 3486 (74 %) of them real and 1223 (26 %) simulated. This makes the AMBAR trial the largest randomized, controlled clinical trial of plasma exchange performed to date for a single disease [134]. Results at the final study visit after 14 months of treatment showed a slower decline or stabilization of disease symptoms in AD patients compared to the placebo group. This was measured by two co-primary outcomes, one cognitive and one functional: the AD Cooperative Study-Activities of Daily Living (ADCS-ADL) scale (52 % less decline; p = 0.03); ADAS-cog scale (66 % less decline; p = 0.06), and in the two global assessment scales: Clinical Dementia Rating Sum of Boxes (CDR-Sb) scale (71 % less decline; p = 0.002), and AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) scale (100 % less decline; p < 0.0001).

The beneficial effect was particularly evident in the moderate AD cohort (baseline MMSE 18–21) as compared with the milder cohort (baseline MMSE 22–26) for the two co-primary outcomes. However, for the two global assessment scales both cohorts, mild and moderate, performed better than placebo [134]. Biomarker measures highlighted a decrease of CSF $A\beta_{42}$ levels in the placebo group at the end of the treatment period particularly in the moderate group compared with the group treated with plasma exchange which remained stable (p = 0.05). Procedures were feasible and well-tolerated with nearly 90 % of the 4709 apheresis sessions being uneventful. The adverse event profile was as expected for patients undergoing plasma exchange [134].

Secondary clinical endpoints included changes from the baseline scores in several neuropsychological and quality-of-life tests [133]. Preliminary communications have reported that the all-patient and mild AD cohorts treated with PE and high-dose albumin plus IVIG showed improvement in language fluency and processing speed at the end of the study. The all-patient and moderate AD cohorts showed significantly improved short-term verbal memory. By contrast, neuropsychological and quality-of-life scores for placebo patients declined across the study period [146]. Also, in preliminary communications, neuroimaging studies using positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) technique showed positive results particularly in patients receiving both albumin and immunoglobulin. In comparison with the placebo group, these patients had less reduction in brain glucose metabolism over the 14 months of the clinical trial. This suggests less progression of neuronal damage in these patients [146].

5. Conclusions

To date, there are no pharmacologic treatments available with proven efficacy to inhibit or slow neuronal death associated with the morbidity and mortality of AD. Clinical trials that have focused on amyloid and non-amyloid treatment strategies with small molecules and immunotherapies approaches have accumulated a long list of failures and there are currently very few promising candidates. However, the combination of plasma removal through plasmapheresis and replacement with therapeutic albumin has produced encouraging results. The multiple favorable structural and molecular properties of albumin, as well as its numerous pleiotropic physiologic functions (e.g., circulating Aβ-binding capacity. transporter, detoxifier, antioxidant, immunomodulator, anti-inflammatory), led to the development of the AMBAR clinical program that considered plasma exchange with therapeutic albumin as a multi-targeted therapeutic approach for treating AD. Positive results from the phase 1, 2, an 2b/3 trials which showed improvement in the most relevant clinical endpoints, offer a glimmer of hope to both AD patients and caregivers.

Authors contribution

All authors contributed equally to the preparation of this manuscript.

Declaration of Competing Interest

MC and AP are full-time employees of Grifols, a manufacturer of plasma-derived therapeutic albumin.

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