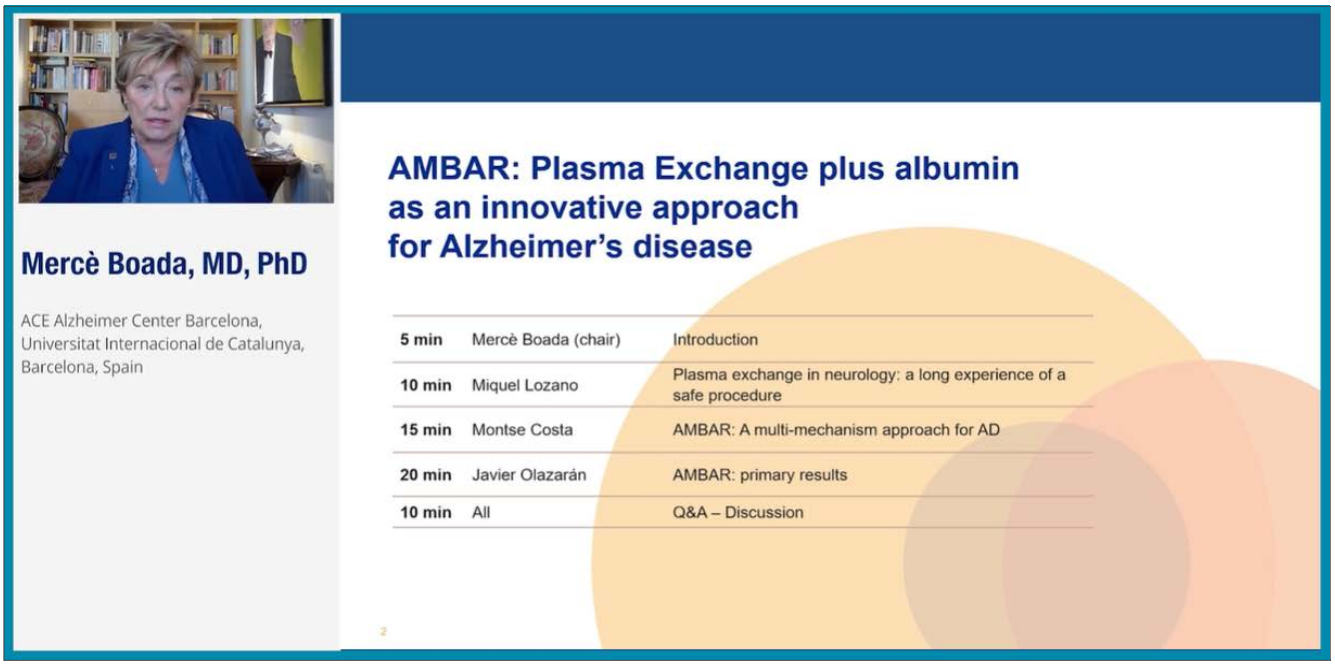
PLASMA EXCHANGE PLUS ALBUMIN FOR ALZHEIMER'S DISEASE: THE AMBAR APPROACH

Report of the Grifols-sponsored symposium "AMBAR: Plasma Exchange plus albumin as an innovative approach for Alzheimer's Disease," presented at the 7th Congress of the European Academy of Neurology (EAN) on 21st June 2021.



Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation in the brain of amyloid-b plaques and the formation of intracellular neurofibrillary tangles of hyperphosphorylated tau.[1,2] The clinical presentation of AD includes a progressive decline in two or more cognitive domains, which include memory, language, executive and visuospatial function, and behavior.[1] These, in turn, can impair the ability to perform instrumental and/or basic activities of daily living.[1]

For many years, the only approved medications for AD were the cholinesterase inhibitors donepezil, galantamine, and rivastigmine,[3-5] and the N-methyl-d-aspartate receptor antagonist memantine.[6] While these treatments are effective in providing symptomatic relief, they are not disease-modifying treatments that can prevent, delay onset, or slow the progression of the disease.[3-6] In June 2021, the US Food and Drug Administration (FDA) granted accelerated approval to the amyloid-β-targeted monoclonal antibody aducanumab for the treatment of AD – the first potentially disease-modifying therapy.[7] Accelerated approval is based on expected clinical benefits, as aducanumab studies did not provide evidence of the effectiveness of the drug and further studies are still required for post-approval verification.[8] Nevertheless, targeting the known pathological hallmarks of a disease is an established therapeutic approach, and combining this with approaches that have shown efficacy in other neurological and inflammatory conditions may provide efficacy above amyloid-b targeting alone.

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Plasma exchange in Alzheimer's disease

Considering that ~90% of circulating amyloid-β is bound to albumin, and that a dynamic equilibrium exists between peripheral and central amyloid-β, plasma exchange (PE) with albumin replacement was proposed as part of a multi-targeted strategy for AD (The AMBAR® approach).[9] Therapeutic PE involves the removal of blood plasma by plasmapheresis and replacing it with an appropriate fluid, usually albumin solution, to eliminate toxic endogenous and exogenous substances (e.g., autoantibodies, alloantibodies, immune complexes, toxins and proteins – such as amyloid-β).[9] PE is generally well-tolerated, with most complications being of mild to moderate severity and easily managed.[9] As such, PE is widely used (according to American Society for Apheresis guidelines) as an evidence-based treatment for various neurological disorders, including Guillain-Barré syndrome, myasthenia gravis, and chronic inflammatory demyelinating polyradiculoneuropathy, as well as other autoimmune and inflammatory conditions.[9,10] By removing circulating amyloid-β by PE and replacing the plasma with an albumin solution, which not only acts as a plasma volume expander but also has numerous other pleotropic functions relevant to AD (e.g., circulating amyloid-β-binding capacity, transporter, detoxifier, antioxidant), it was hoped that central amyloid-β could be reduced and the course of the disease modified.

Based on this rationale, a preliminary pilot study of PE with albumin replacement (EudraCT identifier: 2005-001616-45) was conducted in 2005 and a Phase 2 trial (EudraCT identifier: 2007-000414-36; NCT00742417) conducted in 2007.[11,12] Results from these studies demonstrated that memory and language decline could be slowed in patients with AD, and that the effects on cognition were persistent for up to 44 weeks after PE was stopped.[2,11] Because of these promising results, further investigation of the procedure was pursued.

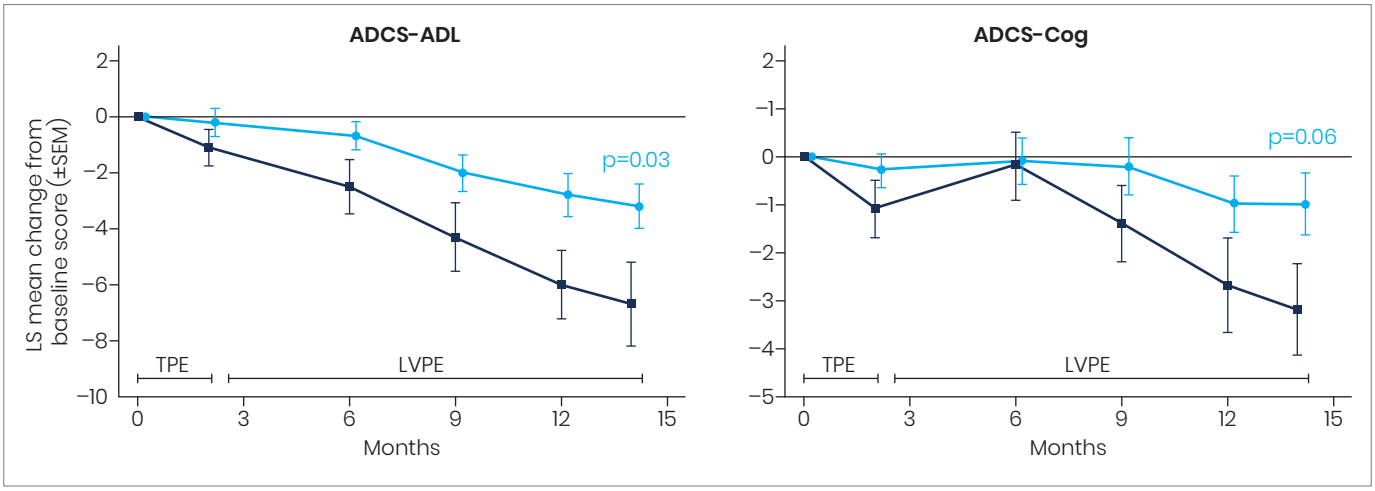
The AMBAR study

The Alzheimer's Management By Albumin Replacement (AMBAR; NCT01561053) study was a Phase 2b/3, international, multicentre, randomised, double-blind, placebo-controlled trial investigating the use of PE in patients with mild-to-moderate AD from 41 sites across Spain and the Unites States.[2] In total, 347 patients were randomised 1:1:1:1 to receive (i) PE with low-albumin (20 g), (ii) PE with low albumin (20 g) alternated with intravenous immunoglobulin (IVIG; 10g), (iii) high albumin (40 g) alternated with high IVIG (20 g), or (iv) placebo.[2] The procedure involved an initial 6-week period of conventional PE sessions (performed weekly), followed by a 12-month period of low-volume PE sessions (LVPE); performed monthly.[2] There were two co-primary efficacy outcomes: the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog).[2] Secondary outcomes included two global assessments of change: the Clinical Dementia Rating Sum of Boxes (CDR-sb) and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).[2]

After 14 months, PE had significantly reduced functional decline by 52% vs placebo (ADCS-ADL difference: 3.5 points; p=0.03) and cognitive decline by 66% vs placebo (ADAS-cog difference: -2.1 points; p=0.06; **Figure 1**).[2] Similarly, PE significantly reduced global decline vs placebo as measured by both CDR-sb (71% reduction; p=0.002) and ADCS-CGIC (100% reduction; p<0.001).[2] When separated by AD severity ('mild': Mini-Mental State Examination [MMSE] = 22–26; 'moderate': MMSE = 18–21), it was found that ADCS-ADL and ADAS-cog decline were both reduced by 61% vs placebo in patients with moderate AD (p=0.02 and p=0.05, respectively); in patients with mild AD, the scores remained stable for both PE and placebo groups throughout the study.[2]

Of all the 4,709 PE procedures performed during the AMBAR study, only 10.6% were associated with any adverse events (AEs), with the most common AEs being local catheter reactions (2.4%).[2] AEs were usually transient and few were considered related to the study product (0.3–1.4% across PE treatment arms).[2] Most AEs occurred during the more intensive 6-week therapeutic PE period, with fewer occurring during the 12-month LVPE period. Both the percentage of patients withdrawing from the study (28%) and the mortality rate (0.6%) were consistent with the rates for PE reported in other studies.[2]

Figure 1. Change from baseline in function (ADCS-ADL) and cognition (ADAS-cog) outcomes for all combined PE treatment arms compared with placebo (AMBAR study).[2]



ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; LS, least squares; LVPE, low-volume plasma exchange; PE, plasma exchange; SEM, standard error of the mean; TPE, therapeutic plasma exchange.

Summary

For many years, only donepezil, galantamine, rivastigmine, and memantine were approved for use in AD, but these treatments only provide symptomatic relief. However, the results of the AMBAR study show potentially disease-modifying effects with PE, helping to prevent or slow the progression of the disease. As a result of these findings, the first AMBAR® clinical centre has recently been opened in Barcelona in collaboration with the ACE Alzheimer Centre, with the aim of providing the most comprehensive patient care for people with AD and their caregivers.

This report was developed as part of a touchSYMPOSIUM HIGHLIGHTS activity. To view the full touchSYMPOSIUM HIGHLIGHTS activity, please visit: www.touchneurologytmc.com/alzheimers-disease-dementia/learning-zone/plasma-exchange-plus-albumin-for-alzheimers-disease/

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