Neuropsychological, neuropsychiatric, and quality-of-life assessments in Alzheimer’s disease patients treated with plasma exchange with albumin replacement from the randomized AMBAR study

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Abstract

Introduction: We report the effects of plasma exchange (PE) with albumin replacement on neuropsychological, neuropsychiatric, and quality-of-life (QoL) outcomes in mild-to-moderate Alzheimer’s disease (AD) patients in a phase 2b/3 trial (Alzheimer’s Management by Albumin Replacement [AMBAR] study).

Methods: Three hundred forty-seven patients were randomized into placebo (sham-PE) and three PE-treatment arms with low/high doses of albumin, with/without intravenous immunoglobulin (IVIG). Specific test measurements were performed at baseline; month 2 (weekly conventional PE); months 6, 9, and 12 (monthly low-volume PE [LVPE]); and month 14.

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Results: The PE-treated mild-AD cohort improved their language fluency and processing speed versus placebo at month 14 (effect sizes: > 100%; P-values: .03 to .001). The moderate-AD cohort significantly improved short-term verbal memory (effect sizes: 94% to >100%; P-values: .02 to .003). The progression of the neuropsychiatric symptoms of PE-treated was similar to placebo. Mild-AD patients showed improved QoL (P-values: .04 to .008).

Discussion: PE-treated AD patients showed improvement in memory, language abilities, processing speed, and QoL-AD. No worsening of their psychoaffective status was observed.

KEYWORDS albumin, albutein, Alzheimer’s disease, clinical trial, plasma exchange, plasmapheresis

1 INTRODUCTION

Brain damage and neuronal loss that characterize Alzheimer’s disease (AD) lead to episodic memory loss as well as additional cognitive impairment including deficits in attention, concentration, visuospatial ability, mental processing speed, executive function, verbal fluency, and speech and language skills. Worsening of such cognitive symptoms accelerates in both severity and frequency as AD progresses, which can result in social exclusion and a decrease in the quality of life for patients, caregivers, and family members.

Existing approved therapeutic approaches to AD are symptomatic, aimed at transiently slowing the progression of symptoms by modulating neurotransmission-cholinesterase inhibitors and N-methyl-d-aspartate receptor antagonists (memantine). To date, clinical trials studying small molecule pharmacotherapy and immunotherapies have not demonstrated relevant effects on cognition and/or functional performance.

Plasma exchange (PE) with albumin replacement is being investigated as a new therapeutic approach for AD. AD patients’ plasma contains amyloid beta (Aβ) protein bound to circulating albumin as well as highly oxidized and glycated albumin that impairs albumin antioxidant action. It is hypothesized that routine PE-removal of AD patient’s plasma—containing albumin-bound Aβ—might change the dynamic equilibrium of Aβ between cerebrospinal fluid (CSF) and plasma, which would increase the transport of free Aβ from CSF to plasma.

The AMBAR (Alzheimer Management by Albumin Replacement) trial (EudrACT#: 2011-001598-25; ClinicalTrials.gov ID: NCT01561053) tested PE with different replacement doses of albumin, with or without intravenous immunoglobulin (IVIG) to correct a possible immunological deficit, in mild-to-moderate AD patients. Recently, results of the primary endpoints of the AMBAR trial have been reported. Results demonstrated that PE treatment could slow down the decline of cognitive, functional, and global assessments in AD. Here we present the results of the neuropsychological (including memory, language, and attention/executive functions), neuropsychiatric (including depression and suicide), and quality-of-life (QoL) outcomes of the AMBAR study.

2 METHODS

2.1 Patients

The study population consisted of the 322 patients from the AMBAR study, 54% women and 46% men, with average age of 69.0 ± 7.7 years. They were diagnosed with AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and had an average Mini-Mental State Examination (MMSE) score of 21.26 ± 2.6. At screening, patients were being treated with a stable dose of cholinesterase inhibitors and/or memantine and were free of cerebrovascular disease. Further details of demographic and clinical characteristics of patients are available elsewhere and summarized in Table S1 in supporting information.

Both the patient and a close relative or legal representative read and signed the informed consent document prior to participation in the trial. The study was approved by the institutional review boards or ethics committees from the sites and the health authorities.

2.2 Treatment study groups

Patients in the AMBAR study were randomly distributed into one placebo group (N = 80) undergoing placebo procedures and three groups receiving PE with different replacement doses of albumin (albumtein, Grifols) and IVIG (flebogamma 5% DIF, Grifols): “low-albumin” group (N = 78), ”low-albumin+IVIG” group (N = 86), and ”high-albumin+IVIG” group (N = 78). The patients, caregivers, and raters were blinded to the treatment received. Further details of randomization and masking (placebo procedures) of the AMBAR study are available elsewhere.
2.3 | Plasma exchange administration schedule

The three active groups first underwent a 6-week period of treatment with 1 weekly session of conventional therapeutic PE (TPE) with albumin 5% replacement. After this first period, the three groups underwent a second 12-month period with one session per month of low-volume PE (LVPE) with albumin 20%, distributed as follows: infusion of 20 g albumin in the “low-albumin” group; infusion of 20 g albumin alternated with infusions of 10 g IVIG in the “low-albumin+IVIG” group; and infusion of 40 g albumin alternated with infusions of 20 g IVIG in the “high-albumin+IVIG” group. The placebo group received the same schedule but with simulated PE through a noninvasive placebo procedure that mimicked real PE (sham-PE). Full details of the interventions are available elsewhere.23,24

2.4 | Objective and outcomes

The objective of the study was the assessment of the effects of PE treatment on neuropsychological, neuropsychiatric, and QoL outcomes in mild-to-moderate AD patients (secondary clinical endpoints of the AMBAR study).23 To this end, specific test measurements were performed across the study at defined time points as follows: at month 0 (baseline visit); at month 2 (intermediate visit; after the TPE treatment period); at months 6, 9, and 12 (during the LVPE treatment period); and at month 14 (final visit).

Population was tested as whole ("all-patient" population) as well as dichotomized into mild and moderate AD cohorts (both N = 161) based on baseline MMSE scores. Because baseline AD severity of our sample (MMSE 18–26) was globally milder than traditionally considered for mild-to-moderate AD (MMSE 10–23),26 in this study baseline MMSE scores 22 to 26 were considered mild impairment and 18 to 21 moderate impairment.

Efficacy variables included the change from baseline to the defined time points as measured with a neuropsychological test battery, a set of neuropsychiatric tests, and QoL tests.

2.5 | Specific tests

The neuropsychological battery comprised: Rey Auditory Verbal Learning Test (RAVLT),27 Phonetic Verbal Fluency (PVF), and Semantic Verbal Fluency (SVF)28 tests; Neuropsychological Assessment Battery naming test (NAB-NT);29 and Symbol Digit Modalities Test (SDMT).30 RAVLT consists of a list of 15 words presented in the same order that the subject listens to and must remember and repeat according to 5 scores (1: immediate recall—i.e., sum of recall in five consecutive trials; 2: interference; 3: short delay recall; 4: long delay recall; and 5: recognition memory). PVF and SVF tests allow language/attention assessment through voluntary access to a certain vocabulary assessing reduction in verbal spontaneity and fluency difficulties. NAB-NT is designed to highlight deficits in visual confrontation naming skills and to identify aphasia. SDMT was developed principally for examining visual attention and tracking, concentration, and psychomotor speed.

Neuropsychiatric and psychoaffective assessments included: Neuropsychiatric Inventory (NPI) test, to evaluate the most frequent neuropsychiatric manifestations of dementia and also to determine their frequency and severity;31 and Cornell Scale for Depression in Dementia (CSDD) to evaluate the signs and symptoms of major depression in patients with dementia.

The Quality of Life-Alzheimer’s Disease (QoL-AD) scale is designed specifically to obtain a rating of the quality of life from both the patient and the caregiver.22

RESEARCH IN CONTEXT

1. Systematic Review: Recently, results of the main endpoints of the phase 2b/3 AMBAR (Alzheimer’s Management by Albumin Replacement) trial have demonstrated that plasma exchange (PE) with albumin replacement slowed down the decline of cognitive, functional, and global assessments in Alzheimer’s disease (AD).

2. Interpretation: Clinical secondary endpoints of the AMBAR trial show that PE-treatment (particularly the high albumin+intravenous immunoglobulin arm) significantly improved the language fluency and processing speed capacities of mild AD (Mini-Mental State Examination [MMSE]: 22–26) patients, and the short-term verbal memory of moderate AD (MMSE: 18–21) patients. These effects were accompanied by a positive impact on AD patients’ quality of life and were not associated with a worsening of their neuropsychiatric nor psychoaffective status.

3. Future Directions: These findings confirm the potential of PE with albumin replacement as a new modality of treatment in AD that was suggested by the main outcomes. Further analyses and new studies are in progress.

HIGHLIGHTS

- Alzheimer’s disease patients were treated with plasma exchange+albumin replacement.
- Treated patients with mild disease improved their language fluency and processing speed.
- Treated patients with moderate disease improved their short-term verbal memory.
- Psychoaffective status of patients was stable and their quality of life improved.
### TABLE 1  Distribution of patients among treatment arms and Alzheimer’s disease severity cohort

| Treatment arm/AD severity cohort | PE treatment |  |
|---------------------------------|-------------|---|
|                                 | Low albumin | Low albumin + IVIG | High albumin + IVIG | All PE treated | Placebo | Total |
| Moderate AD (MMSE 18–21)        | 46          | 37                        | 42                  | 125             | 36       | 161  |
| Mild AD (MMSE 22–26)            | 32          | 49                        | 36                  | 117             | 44       | 161  |
| All-patient                     | 78          | 86                        | 78                  | 242             | 80       | 322  |

Abbreviations: AD, Alzheimer’s disease; IVIG, intravenous immunoglobulin; MMSE, Mini-Mental State Examination; PE, plasma exchange with albumin replacement.

### 2.6  Statistics

The secondary efficacy endpoints (change from baseline to 2, 6, 9, 12, and 14 months) in all tests were analyzed using analysis of covariance (ANCOVA) with treatment group as a fixed effect, and the corresponding baseline value, age, and AD severity as covariates. The differences from the placebo group were estimated using least square (LS) means (with 95% confidence interval [CI] or ± standard error of the mean [SEM]). Sample size of 312 patients (78 in each of the four groups) was calculated for the primary endpoints as already reported.23,24

Because all treated patients shared the same plasma removal component of PE regardless of the group allocation, the three treatment groups were also pooled and analyzed as the combined treatment group (PE-treated group). The same approach was performed on the two pre-specified AD severity subgroups: moderate AD (baseline MMSE: 18–21) and mild AD (baseline MMSE: 22–26).

Effect size was calculated as the ratio of the difference in percentage change from baseline between the placebo and treated groups over the change from baseline of the placebo group. Effect sizes < 100% indicate less decline compared to placebo while effect sizes > 100% indicate improvement over baseline. Further details on statistics are available elsewhere.23

### 3  RESULTS

Distribution of patients among treatment arms and AD severity cohorts is shown in Table 1. A total of 496 patients were screened (April 2012 to December 2016), 347 patients were randomized, and 322 patients received treatment.

#### 3.1  Verbal learning and memory

The RAVLT 1 (immediate recall) scores in the PE-treated patients showed a trend to stabilization at the end of the conventional PE period (month 2; difference: 1.4 [95% CI: −0.05, 2.85]; P = .06) as well as a slower decline at month 14 (difference: 2.2 [95% CI: −0.16, 4.56]; P = .07; effect size: 55%, less decline; Figure 1A).

When the different treatment modalities were examined, there was a statistically significant difference at month 2 for the low-albumin+IVIG group (difference: 2.0 [95% CI: 0.35, 3.65]; P = .02) and the high-albumin+IVIG group (difference: 2.0 [95% CI: 0.09, 3.91]; P = .03), and for the high-albumin+IVIG group at month 14 (difference: 4.4 [95% CI: 1.26, 7.54]; P = .004; effect size: >100%; improvement; Figure 1D). The effect of PE treatment was more apparent between months 12 and 14 for patients with moderate AD (Figures 1B and 1E), and more apparent between months 2 and 6 for patients with mild AD (Figures 1C and 1F), especially in low-albumin+IVIG and high-albumin+IVIG groups.

The pattern observed for RAVLT 3 (short delay recall) scores was similar to that seen for RAVLT 1 (Figures 2A-2F). However, the scores in interference, long delay recall, and recognition memory (RAVLT 2, 4, and 5, respectively) were not significantly different between treated and placebo patients (Figures S1, S2, and S3 in supporting information, respectively).

#### 3.2  Language fluency

The PVF test scores in the placebo group of the all-patient population declined over the treatment period, whereas values were stable or improved in the PE-treated patients, with a large and significant effect at month 14 (difference: 2.8 [95% CI: 0.66, 4.94]; P = .007; effect size: >100%, improvement; Figure 3A). The high-albumin+IVIG group showed consistent improvement at month 14 (difference: 3.5 [95% CI: 0.52, 6.48]; P = .008; effect size: >100%, improvement). Improvement was slightly less marked in the low-albumin+IVIG group (difference: 3.0 [95% CI: 0.57, 5.43]; P = .02; effect size: >100%, improvement; Figure 3D). Results were even more marked in the population of mild AD patients (Figures 3C and 3F, versus Figures 3B and 3E of moderate AD patients), in which the positive difference from placebo in mean change from baseline for the high-albumin+IVIG group reached up to 6.2 points at month 12 (95% CI: 1.93, 10.47; P = .002) and 4.7 points difference at month 14 (95% CI: −0.21, 9.61; P = .03; effect size: >100%, improvement; Figure 3F). A similar positive pattern of results was noted in the SVF test (Figures 4A-4F).

Mean change from baseline scores in NAB-NT showed no statistically significant differences between placebo and treated groups across the study (Figure S4 in supporting information).

#### 3.3  Mental processing speed

The SDMT mean change from baseline in the all-patient population decreased over the treatment period in the placebo group, while values increased in the group of PE-treated patients at month 14.
**FIGURE 1** Rey Auditory Verbal Learning Test 1 (RAVLT 1; immediate recall) scores in Alzheimer’s disease (AD) patients (all-patient [panels A, D], moderate AD [panels B, E], and mild AD [panels C, F] populations) treated with plasma exchange (PE) with albumin replacement. TPE denotes the 2-month period of conventional therapeutic PE; LVPE denotes the 12-month period of low-volume PE. Statistical significance ($P < .05$) and borderline significance ($P < .1$) between the treated patient groups (low/high albumin dose, with/without intravenous immunoglobulin [IVIG; $n = 78–86$] pooled [panels A-C] or separately [panels D-F]) and the placebo group ($n = 80$) at months 2, 6, 9, 12, and 14, is shown.

**FIGURE 2** Rey Auditory Verbal Learning Test 3 (RAVLT 3; short delay recall) scores in Alzheimer’s disease (AD) patients (all-patient [panels A, D], moderate AD [panels B, E], and mild AD [panels C, F] populations) treated with plasma exchange (PE) with albumin replacement. TPE denotes the 2-month period of conventional therapeutic PE; LVPE denotes the 12-month period of low-volume PE. Statistical significance ($P < .05$) and borderline significance ($P < .1$) between the treated patient groups (low/high albumin dose, with/without intravenous immunoglobulin [IVIG; $n = 78–86$] pooled [panels A-C] or separately [panels D-F]) and the placebo group ($n = 80$) at months 2, 6, 9, 12, and 14, is shown.
FIGURE 3  Phonetic Verbal Fluency test (PVF) scores in Alzheimer's disease (AD) patients (all-patient [panels A, D], moderate AD [panels B, E], and mild AD [panels C, F] populations) treated with plasma exchange (PE) with albumin replacement. TPE denotes the 2-month period of conventional therapeutic PE; LVPE denotes the 12-month period of low-volume PE. Statistical significance ($P < .05$) and borderline significance ($P < .1$) between the treated patient groups (low/high albumin dose, with/without intravenous immunoglobulin [IVIG; $n = 78-86$]) pooled [panels A-C] or separately [panels D-F]) and the placebo group ($n = 80$) at months 2, 6, 9, 12, and 14, is shown.

FIGURE 4  Semantic Verbal Fluency test (SVF) scores in Alzheimer's disease (AD) patients (all-patient [panels A, D], moderate AD [panels B, E], and mild AD [panels C, F] populations) treated with plasma exchange (PE) with albumin replacement. TPE denotes the 2-month period of conventional therapeutic PE; LVPE denotes the 12-month period of low-volume PE. Statistical significance ($P < .05$) and borderline significance ($P < .1$) between the treated patient groups (low/high albumin dose, with/without intravenous immunoglobulin [IVIG; $n = 7886$]) pooled [panels A-C] or separately [panels D-F]) and the placebo group ($n = 80$) at months 2, 6, 9, 12, and 14, is shown.
FIGURE 5  Symbol Digit Modalities Test (SDMT) scores in Alzheimer’s disease (AD) patients (all-patient [panels A, D], moderate AD [panels B, E], and mild AD [panels C, F] populations) treated with plasma exchange (PE) with albumin replacement. TPE denotes the 2-month period of conventional therapeutic PE; LVPE denotes the 12-month period of low-volume PE. Statistical significance (P < .05) and borderline significance (P < .1) between the treated patient groups (low/high albumin dose, with/without intravenous immunoglobulin [IVIG; n = 78–86] pooled [panels A-C] or separately [panels D-F]) and the placebo group (n = 80) at months 2, 6, 9, 12, and 14, is shown (difference: 2.4 [95% CI: –0.36, 5.16]; P = .05; effect size: >100%, improvement; Figures 5A-5F). Among the three PE treatment arms, only the value for the high-albumin+IVIG group was statistically different from placebo at month 14 (difference: 3.5 [95% CI: –0.63, 7.63]; P = .03; effect size: >100%, improvement). In the mild AD patient population there were 3.6 points difference from the placebo in the PE-treated group combined at month 14 (95% CI: –0.70, 7.90; P = .06; effect size: >100%, improvement), and 5.2 points difference from the placebo in the high-albumin+IVIG group (95% CI: –1.88, 12.28; P = .04; effect size: >100%, improvement).

3.4 | Neuropsychiatric status

Globally, there were no marked differences between placebo and the PE treated group in mean change from baseline of NPI total rating and NPI caregiver distress (Figures S5 and S6 in supporting information), as well as in CSDD scale (Figure S7 in supporting information). Moderate AD patients tended to show a flatter progression (i.e., no mean change from baseline across the study) than mild AD patients, who seemed to evolve toward having fewer neuropsychiatric events as well as being less depressed.

3.5 | Quality of life

The mean change from baseline to month 14 in the QoL-AD scores (patient rating) was significantly better in the PE-treated patients compared to placebo in the pooled (Figure 6A) and mild AD (Figure 6C) patients, with a difference of 1.4 points (95% CI: 0.09, 2.71; P = .02; effect size: >100%, improvement) and 2.0 points (95% CI: 0.32, 3.68; P = .01), respectively. In the caregiver rating QoL-AD, significance at month 14 was borderline, with a difference of 1.1 points (95% CI: –0.34, 2.54; P = .09; effect size: >100%, improvement) in the pooled patients (Figure 6D), and 1.5 points (95% CI: –0.35, 3.35; P = .07; effect size: >100%, improvement) in mild AD patients (Figure 6F). In moderate AD patients the differences were non significant (Figures 6B and 6E). Neither in patient rating nor in caregiver rating was there a consistent pattern of improvement associated with treatment arms (Figure S8 in supporting information).

4 | DISCUSSION

Recently, a positive effect of PE on measures of cognition and function (Alzheimer’s Disease Assessment Scale-Cognitive subscale [ADAS-Cog] and Alzheimer’s Disease Cooperative Study-Activities of Daily Living [ADCS-ADL] scale), and on global assessment scores (Clinical Dementia Rating Sum of Boxes [CDR-SB] and the Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change [ADCS-CGIC]) has been reported in mild-to-moderate AD patients in a 14-month study. In these patients the progression of the disease either slowed down or stabilized. As a part of the same clinical trial (AMBAR), we demonstrated here that PE treatment was also associated with positive effects on neuropsychological condition and QoL.
Qualitative Test Battery Results

Our results with a neuropsychological test battery showed statistically significant improvement with respect to placebo (i.e., effect size > 100% in change from baseline scores) in specific AD severity subgroups and treatment arms, typically at more than one assessment time point. This means that PE-treated patients not only did not show the intellectual decline typically associated with the progression of the AD disease but could even be able to learn and recover. Moreover, in several cases, the trend was observed as early as a peak in month 2, the end of conventional, and more intensive, PE period. Overall, our neuropsychological battery results suggest that AD patients could get benefit from PE even at the early stages of AD. Because mild AD patients typically have less insoluble Aβ deposits in the brain, it is suggested that mechanisms beyond removal of albumin-bound Aβ may have been involved in the PE approach, such as elimination of dysfunctional oxidized and glycated albumin, inflammatory mediators, and other proteins, both known and unknown, including possible proaging factors.

Moderate AD patients showed statistically significant differences with respect to placebo in immediate verbal memory (RAVLT 1) at month 14. Mild AD patients also showed significant differences in language fluency (PVF and SVF) and processing speed (SDMT). These results might be related to the SPECT neuroimaging results from the phase 2 study, in which an increase in perfusion of Brodmann areas BA38-R and -L, and BA46-R (specific areas involved in working memory and language function) was observed in PE-treated subjects compared to placebo. By contrast, NAB-NT test results of both placebo and treatment groups did not change significantly across the study. A possible explanation for this apparent variability in the response to the treatment is the lack of sensitivity to detect change by different tests at different stages of AD. An alternative explanation is that PE may differentially affect mild and moderate AD patients depending on the underlying damage associated with different disease stages. Similarly, as AD progresses, patients tend to have more difficulty completing more complex tests. In essence, neuropsychological traits could be a better measure of early synaptic plasticity deficits that can be reversed based on albumin replacement therapy.

In agreement with our results, PVF, SVF, and SDMT seemed to be impaired in the early stages of AD, while RAVLT delayed recall may be a predictor of conversion from mild cognitive impairment to AD. In our RAVLT 1 results, the decline slope in the placebo group was steeper in moderate AD patients. PE effects in this cohort could be seen in the long term (at 12 and 14 months) whereas in mild AD patients, in whom language is less affected (flatter slope), effects were instead seen at 2 and 6 months, after the more intensive TPE period. Moreover, the decline slope in RAVLT 1 score in the placebo group of moderate AD relative to mild AD patients was the steepest in all tests performed. RAVLT 1 was the only task where moderate PE-treated AD patients showed better performance compared to mild AD in the long term.

While the tests of the primary and global assessment endpoints of the AMBAR trial approached cognition rather nonspecifically, neuropsychological tests addressed in the present article addressed...
specific aspects of cognition (i.e., language, memory, praxis). Here we observed differences between the treatment arms that were not observed in the previous endpoints. The high-albumin+IVIG treatment arm was more frequently associated with statistically significant differences in the change from baseline. This was particularly evident in mild AD patients’ performance on language fluency (PVF and SVF), and processing speed (SDMT) tests. Moreover, in RAVLT 1, and to a lesser extent in RAVLT 3, IVIG supplementation accounted for a good portion of the improvement both in mild and/or moderate AD. In the AMBAR trial, IVIG was administered to ameliorate a potential immunological deficit caused by the PE. In our previous paper, we reported that patients who received IVIG seemed to showed fewer infections. Because infections can be associated with mood-related symptoms and worse cognitive performance, this may explain the better cognitive response in the IVIG-treated patients.

The PE approach did not negatively affect the neuropsychiatric status of patients. Moreover, the apparent reduction of neuropsychiatric manifestations and depression symptoms in mild AD patients could be attributable to the placebo effect, being that moderate AD patients may be less conscious of being administered a treatment. Interestingly, these results confirm that blinding in the placebo group was effective. Placebo effects on neuropsychiatric symptoms and depression of AD patients under therapy have been already reported.

Measures of QoL are of paramount importance in AD because of the devastating impact of the disease on both patients and caregivers. Effects on QoL as measured by the caregiver were better in PE-treated than in the placebo arm, especially in the moderate AD patients. By contrast, the positive effects of PE on QoL based on patients’ rating were seen at month 14, with mild AD patients reporting improvement in QoL, but not those with moderate AD. This is consistent with AD progression and the ADCS-ADL results in the AMBAR study, because patients with more advanced stage become unaware of their cognitive and functional limitations.

Our results share similar limitations to those reported for the primary endpoints of the AMBAR trial. Patients were enrolled based on the presence of the AD clinical syndrome, not on the presence or absence of a biomarker. In addition, although the blinding procedure might not, at first, be considered perfect, we have results that suggest binding was effective. Finally, this study was not designed to determine a specific mechanism of action associated with PE beyond the assumed Aβ-albumin binding.

In summary, PE with albumin replacement was able to slow down the decline in neuropsychological capacities associated with AD progression. Importantly, in some cases a trend toward improvement was observed. The moderate AD patient cohort showed an improvement in verbal memory while the mild AD patient cohort was characterized by a better response in language fluency and processing speed. The high-albumin+IVIG treatment arm was more frequently associated with stabilization and improvement across outcomes. These effects were accompanied by a positive impact on patient’s QoL and were not associated with a worsening of their neuropsychiatric and psychoaffective status.

5 | THE AMBAR TRIAL GROUP

In addition to those mentioned as nominal authors, the following investigators and centers enrolled patients into the study: José Lima (American Red Cross Southern Blood Services Region, Atlanta, GA, USA), Juan Pablo Tartari (Hospital Universitari Mutua de Terrassa, Terrassa, Spain), Teresa Moreno (Hospital Clinico San Carlos, Madrid, Spain), Francesc Pujadas (Hospital Vall d’Hebron, Barcelona, Spain), Miguel Goñi (Hospital Universitario de Burgos, Burgos, Spain), José Del Gádándara (Quantum Laboratories, Inc. Wixom, MI, USA), William A. McElvain (Bradenton Research Center, Inc., Bradenton, FL, USA), Ramon Reñé (Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Spain), Secundino López-Pousa (Parc Hospitalari Màrti i Julià, Salt, Spain), Antonio Del Olmo (Hospital Universitario Dr. Peset, Valencia, Spain), Douglas Young (Northern California Research, Sacramento, CA, USA), Babak Tousi (Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA), Jacobo Mintzer (Roper Saint Francis Healthcare, Charleston, SC, USA), Joshua Shua-Haim (Mid-Atlantic Geriatric/ARC, Manchester, NJ, USA), Kimball Johnson (iResearch Atlanta, LLC, Decatur, GA, USA), Ernest Balaguer (Hospital General de Catalunya, Sant Cugat del Valles, Spain), Sarah Berman (University of Pittsburgh Alzheimer Disease Research Center-ADRC, Pittsburgh, PA, USA), Bridge Bellinger (DMI Research, Pinellas Park, FL, USA), Antonio Oliveros (Hospital Viamed Montecanal, Zaragoza, Spain), Norberto Rodríguez (Hospital Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain), Dana Kunjiyan (RTR Medical Group, Savannah, GA, USA), Jordi Alom (Hospital General de Elche, Elx, Spain), César García Pérez-Cejuela (Hospital de Vinalopó, Elx, Spain), Tilo Bertorini (Neurology Clinic, PC, Cordoba, TN, USA), Bennet Machanic (Mountain View Clinical Research, Inc., Denver, CO, USA), Thomas Obisesan (Howard University College of Medicine, Washington, DC, USA), Krzysztof Bujarski (Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA), Mireia Torres and Natalia Afonso (Grifols, Barcelona, Spain), Paul Pinciaro (Grifols, NC, USA), María Paricio (Miami Dade Medical Research Institute, Miami, FL, USA), Lisa McLaughlin (American Red Cross Southern Blood Services Region, Atlanta, GA, USA), Leonard M. Allende (L&L Research Choices, Inc., Miami, FL, USA).

ACKNOWLEDGEMENTS

Michael James PhD, (Grifols) is acknowledged for editorial assistance and careful revision of the text. The contribution of the plasmapheresis nurses and the health-care professionals is deeply appreciated. Deepest thanks from the authors to the patients and their families for their indispensable contribution. The AMBAR study is sponsored by Grifols, a manufacturer of therapeutic human serum albumin and intravenous immune globulin.

CONFLICTS OF INTEREST

Merce Boada has been a consultant for Araclon, Avid, Bayer, Elan, Grifols, Janssen/Pfizer, Lilly, Neuroptix, Nutricia, Roche, Sanofi, Biogen, and Servier; and received fees for lectures and funds for research from Araclon, Esteve, Grifols, Janssen, Novartis, Nutricia, Piramal, Pfizer-Wyett, Roche and Servier. Oscar L. Lopez has been a consultant for...
Grifols and Lundbeck. Javier Olazaran has been a consultant for Schwabe and Grifols; and received fees for lectures and funds for research from Nutricia. Zbigniew M. Szczepiorkowski has been a consultant for Grifols and Fresenius-Kabi and participated in research supported by funds from Grifols and Fresenius-Kabi. Merce Boada, Gerard Pinol-Rlegret, Jose E. Gamez, Fernando Anaya, PO, Dobri Kiprov, and SH received funding from Grifols to perform this study. Laura Nunez, Montserrat B. Alegret, Carlota Grifols, Jordi Bozzo, and Antonio Paez are full-time employees of Grifols.

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REFERENCES
1. Mukherjee S, Mez J, Trirschuh EH, et al. Genetic data and cognitively defined late-onset Alzheimer’s disease subgroups. Mol Psychiatry. 2018;25(11):2942-2951.
2. Lawton MP. Quality of life in Alzheimer disease. Alzheimer Dis Assoc Disord. 1994;8(3):138-150.
3. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil. JAMA. 2004;291:317.
4. Kemp PM, Holmes C, Hoffmann S, et al. A randomised placebo controlled study to assess the effects of cholinergic treatment on muscarinic receptors in Alzheimer’s disease. J Neurol Neurosurg Psychiatry. 2003;74:1567-1570.
5. Atri A, Frölich L, Ballard C, et al. Effect of idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer disease. JAMA. 2018;319:130.
6. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer’s disease. N Engl J Med. 2014;370:311-321.
7. Egan MF, Kost J, Tariot PN, et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer’s disease. N Engl J Med. 2018;378:1691-1703.
8. Egan MF, Kost J, Voss T, et al. Randomized trial of verubecestat for prodromal Alzheimer’s disease. N Engl J Med. 2019;380:1408-1420.
9. Honig LS, Vellas B, Woodward M, et al. Trial of solanezumab for mild dementia due to Alzheimer’s disease. N Engl J Med. 2018;378:321-330.
10. Ostrowitzki S, Lasser RA, Dorflinger E, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer’s disease. Alzheimers Res Ther. 2017;9:95.
11. Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapinezuam in mild-to-moderate Alzheimer’s disease. N Engl J Med. 2014;370:322-330.
12. Boada M, Anaya F, Ortiz P, et al. Efficacy and safety of plasma exchange with 5% albumin in mild-moderate Alzheimer’s disease patients: a multicenter, randomized, controlled clinical trial. J Alzheimers Dis. 2017;56:129-143.
13. Boada M, Ortiz P, Anaya F, et al. Amyloid-targeted therapeutics in Alzheimer’s disease: use of human albumin in plasma exchange as a novel approach for Abeta mobilization. Drug News Perspect. 2009;22:325-339.
14. Costa M, Ortiz AM, Jorquera JI. Therapeutic albumin binding to remove amyloid-beta. J Alzheimers Dis. 2012;29:159-170.
15. Cuberas-Borros G, Roca I, Boada M, et al. Longitudinal neuroimaging analysis in mild-moderate Alzheimer’s disease patients treated with plasma exchange with 5% human albumin. J Alzheimers Dis. 2018;61:321-332.
16. Milojlocic J, Costa M, Ortiz AM, Jorquera JI, Melacini G. In vitro amyloid-beta binding and inhibition of amyloid-beta self-association by therapeutic albumin. J Alzheimers Dis. 2014;38:753-765.
17. Biere AL, Ostaszewski B, Stimson ER, Hyman BT, Maggio JE, Selkoe DJ. Amyloid beta-peptide is transported on lipoproteins and albumin in human plasma. J Biol Chem. 1996;271:32916-32922.
18. Costa M, Horrillo R, Ortiz AM, et al. Increased albumin oxidation in cerebrospinal fluid and plasma from Alzheimer’s disease patients. J Alzheimers Dis. 2018;63:1395-1404.
19. Ramos-Fernandez E, Tajes M, Palomer E, et al. Posttranslational nitroglycific modifications of albumin in Alzheimer’s disease: implications in cytotoxicity and amyloid-beta peptide aggregation. J Alzheimers Dis. 2014;40:643-657.
20. Colombo G, Clerici M, Giustarini D, Rossi R, Milzani A, Dalle-Donne I. Redox albuminomics: oxidized albumin in human diseases. Antioxid Redox Signal. 2012;17:1515-1527.
21. DeMattos RB, Bales KR, Cummins DJ, Dodart JC, Paul SM, Holtzman DM. Peripheral anti-A antibody alters CNS and plasma A clearance and decreases brain A burden in a mouse model of Alzheimer’s disease. Proc Natl Acad Sci U S A. 2001;98:8850-8855.
22. Marques MA, Kulstad JJ, Savard CE, et al. Peripheral amyloid-beta levels regulate amyloid-beta clearance from the central nervous system. J Alzheimers Dis Rep. 2009;16:325-329.
23. Boada M, Lopez O, Nunez L, et al. Plasma exchange for Alzheimer’s disease Management by Albumin Replacement (AMBAR) trial: study design and progress. Alzheimers Dement (N Y). 2019;5:61-69.
24. Boada M, Lopez O, Olazaran J, et al. A randomized, controlled clinical trial of plasma exchange with albumin replacement for Alzheimer’s disease: primary results of the AMBAR Study. Alzheimers Dement. 2020;16:1412-1425.
25. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer’s disease. Neurology. 1984;34:939-944.
26. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40:922-935.
27. Rey A. L’examen Clinique en Psychologie. Paris: Presses Universitaires de France; 1964.
28. Benton A, Hamsher K. Multilingual Aphasia Examination. Iowa City: ASA Associates; 1983.
29. Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Philadelphia: Lea & Febiger; 1983.
30. Smith A. Symbol Digits Modality Test. Los Angeles: Western Psychological Services; 1973.
31. Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. Neurol. 1997;48:S10-6.
32. Merchant C, Hope KW. The quality of life in Alzheimer’s disease scale: direct assessment of people with cognitive impairment. J Clin Nurs. 2004;13:105-110.
33. Cummings BJ, Cotman CW. Image analysis of beta-amyloid load in Alzheimer’s disease and relation to dementia severity. Lancet. 1995;346:1524-1528.
34. Weinschenker BG, O’Brien PC, Pettersson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 1999;46:878-886.
35. Meca-Lallana JE, Rodriguez-Hilario H, Martinez-Vidal S, et al. Plasmapheresis: its use in multiple sclerosis and other demyelinating processes of the central nervous system. An observation study. Rev Neurol. 2003;37:917-926.
36. Katimsipardi L, Litterman NK, Schein PA, et al. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science. 2014;344:630-634.
37. Villeda SA, Plambeck KE, Middeldorp J, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med. 2014;20:659-663.

38. Alegret M, Cuberas-Borrós G, Vinyes-Junqué G, et al. A two-year follow-up of cognitive deficits and brain perfusion in mild cognitive impairment and mild Alzheimer’s disease. J Alzheimers Dis. 2012;30:109-120.

39. Gainotti G, Quaranta D, Vita MG, Marra C. Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer’s disease. J Alzheimers Dis. 2014;38:481-495.

40. Zhou B, Zhao Q, Kojima S, et al. One-year outcome of shanghai mild cognitive impairment cohort study. Curr Alzheimer Res. 2019;16:156-165.

41. Nikolai T, Bezdicek O, Markova H, et al. Semantic verbal fluency impairment is detectable in patients with subjective cognitive decline. Appl Neuropsychol Adult. 2018;25:448-457.

42. Russo MJ, Campos J, Vazquez S, Sevlever G, Allegri RF. Adding recognition discriminability index to the delayed recall is useful to predict conversion from mild cognitive impairment to Alzheimer’s disease in the Alzheimer’s disease neuroimaging initiative. Front Aging Neurosci. 2017;9:46.

43. Alsina L, Mohr A, Montanes M, et al. Surveillance study on the tolerability and safety of Flebogamma(R) DIF (10% and 5% intravenous immunoglobulin) in adult and pediatric patients. Pharmacol Res Perspect. 2017;5:e00345.

44. Shah FA, Pike F, Alvarez K, et al. Bidirectional relationship between cognitive function and pneumonia. Am J Respir Crit Care Med. 2013;188:586-592.

45. Smith AP. Effects of the common cold on mood, psychomotor performance, the encoding of new information, speed of working memory and semantic processing. Brain Behav Immun. 2012;26:1072-1076.

46. Jacus JP. Awareness, apathy, and depression in Alzheimer’s disease and mild cognitive impairment. Brain Behav. 2017;7:e00661.

47. Bernard K, Gouttefangeas S, Bretin S, et al. A 24-week double-blind placebo-controlled study of the efficacy and safety of the AMPA modulator S47445 in patients with mild to moderate Alzheimer’s disease and depressive symptoms. Alzheimers Dement (N Y). 2019;5:231-240.

48. Hongisto K, Vaattainen S, Martikainen J, et al. Self-Rated and caregiver-rated quality of life in Alzheimer disease with a focus on evolving patient ability to respond to questionnaires: 5-year prospective ALSOVA Cohort Study. Am J Geriatr Psychiatry. 2015;23:1280-1289.

49. Lopez OL, Becker JT, Somsak D, Dew MA, DeKosky ST. Awareness of cognitive deficits and anosognosia in probable Alzheimer’s disease. Eur Neurol. 1994;34:277-282.

**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

**How to cite this article:** Boada M, López OL, Olazarán J, et al. Neuropsychological, neuropsychiatric, and quality-of-life assessments in Alzheimer’s disease patients treated with plasma exchange with albumin replacement from the randomized AMBAR study. Alzheimer’s Dement. 2022;18:1314–1324. [https://doi.org/10.1002/alz.12477](https://doi.org/10.1002/alz.12477)