Neuroimaging analyses from a randomized, controlled study to evaluate plasma exchange with albumin replacement in mild-to-moderate Alzheimer’s disease: additional results from the AMBAR study

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Abstract

Purpose  This study was designed to detect structural and functional brain changes in Alzheimer’s disease (AD) patients treated with therapeutic plasma exchange (PE) with albumin replacement, as part of the recent AMBAR phase 2b/3 clinical trial.

Methods  Mild-to-moderate AD patients were randomized into four arms: three arms receiving PE with albumin (one with low-dose albumin, and two with low/high doses of albumin alternated with IVIG), and a placebo (sham PE) arm. All arms underwent 6 weeks of weekly conventional PE followed by 12 months of monthly low-volume PE. Magnetic resonance imaging (MRI) volumetric analyses and regional and statistical parametric mapping (SPM) analysis on 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) were performed.

Results  MRI analyses (n = 198 patients) of selected subcortical structures showed fewer volume changes from baseline to final visit in the high albumin + IVIG treatment group (p < 0.05 in 3 structures vs. 4 to 9 in other groups). The high albumin + IVIG group showed no statistically significant reduction of right hippocampus. SPM 18FDG-PET analyses (n = 213 patients) showed a worsening of metabolic activity in the specific areas affected in AD (posterior cingulate, precuneus, and parieto-temporal regions). The high-albumin + IVIG treatment group showed the greatest metabolic stability over the course of the study, i.e., the smallest percent decline in metabolism (MaskAD), and least progression of defect compared to placebo.

Conclusions  PE with albumin replacement was associated with fewer deleterious changes in subcortical structures and less metabolic decline compared to the typical of the progression of AD. This effect was more marked in the group treated with high albumin + IVIG.

Trial registration  (AMBAR trial registration: EudraCT#: 2011–001.598-25; ClinicalTrials.gov ID: NCT01561053).

Keywords  Alzheimer’s disease · Plasmapheresis · Plasma exchange · Albumin · Intravenous immunoglobulin

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Introduction

Dementia is a growing public health concern worldwide. It is estimated that the number of people living with dementia will be 131.5 million by 2050 [1]. Alzheimer’s disease (AD) accounts for 60–80% of these cases of dementia [2]. The behavioral symptoms of AD include cognitive impairment, memory loss, depression, and deficits in communication and spatial perception [3]. Microscopically, AD is characterized by neurofibrillary tangles (intracellular) and amyloid plaques (extracellular) made up of phosphorylated tau proteins and amyloid β peptides (Aβ), respectively [4, 5]. Both of these defects are thought to contribute to neuronal cell death.

In the efforts to attack the underlying disease process in AD, one of the primary targets has been Aβ. Accumulation of Aβ in brain tissue and vasculature is thought to be an important part of the AD process [6]. Although the therapeutic strategy of targeting Aβ to improve function in AD patients has been until recently largely unsuccessful [7–9], a potential clinical benefit associated with reduction of Aβ plaques using anti-Aβ antibodies is currently contributing to the understanding of Aβ pathophysiology [10–13]. Furthermore, additional interest in Aβ has been piqued by the observation that sequestration of Aβ in the circulation resulted in a decrease in Aβ in the cerebrospinal fluid (CSF) [14]. This led to the “sink hypothesis” that removal of Aβ from the circulation could lead to a decrease in Aβ in the CSF and the brain.

Given that Aβ in blood is bound to albumin (1:1) [15], it was proposed that plasma exchange (PE) with albumin replacement could be used to remove Aβ from the peripheral circulation. Removal of the patient’s plasma would result in removal of albumin-bound Aβ. PE would be followed by replacement of the lost volume along with exogenous albumin to avoid hypovolemia and maintain osmotic pressure [16]. This could result in further sequestration of Aβ through binding to the fresh Aβ-free [17] albumin. Additional PE could produce further reductions in CSF/brain Aβ through equilibration with plasma Aβ [18].

The neuroimaging studies described in this paper were part of a multicenter, randomized, controlled, phase 2b/3 study to evaluate the efficacy and safety of PE with albumin replacement with or without alternated intravenous immunoglobulin (IVIG) in AD patients (AMBAR Trial: EudraCT#: 2011–001,598-25; ClinicalTrials.gov ID: NCT01561053). In a previous phase 2 study [19], positive clinical changes associated with PE treatment were found to parallel neuroimaging data [20]. Similarly, the previously published clinical results from the AMBAR study showed that PE treatment slowed the decline in cognitive, functional, and neuropsychological outcomes in AD patients, while improving their quality of life [21–23].

Material and methods

Objective and study design

The neuroimaging objective of the AMBAR study was to detect functional and structural changes in the brains of mild-to-moderate AD patients treated with PE with therapeutic albumin replacement in comparison with placebo (sham-PE) patients. These outcomes were assessed using magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET).

The AMBAR trial enrolled patients at 41 sites: 19 in Spain and 22 in the USA. This study was conducted in compliance with all applicable regulatory guidelines and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP). Each patient and caregiver, family member, or legal representative provided informed consent prior to enrollment. The Institutional Review Boards (IRBs) or Ethics Committees from the sites and the Health Authorities from the countries where the study was performed approved the protocol, the informed consent form, and the patient information sheets.

Patient population

In the AMBAR trial, 322 patients were evaluable and 232 patients (72%) completed the study. Reasons for discontinuation are summarized in Supplemental Table S1 for placebo and active treatment groups. Further details have been previously reported elsewhere [23].

Inclusion criteria were men and women between 55 and 85 years of age with a diagnosis of probable AD dementia according to the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria [24], with baseline Mini-Mental State Exam (MMSE) score from 18 to 26 [25], and on a stable dose of AChEIs and/or memantine. Exclusion criteria included cerebrovascular disease, IgA deficiency, low hemoglobin, high plasma creatinine, uncontrolled hypertension, liver disease, heart diseases, any condition in which the treatment was contraindicated or not feasible, and fewer than 6 years of education. Full details of eligibility criteria are available elsewhere [22, 23].

The population was 54% female with an average age of 69.0 ± 7.7 (mean ± SD) years. The patients were equally divided in terms of mild (n = 161, baseline Mini-Mental State Examination [MMSE] score: 22–26) and moderate AD (n = 161, baseline MMSE score: 18–21). Patients were free of cerebrovascular disease and had been diagnosed with AD since 2.4 ± 2.4 years based on criteria from the
NINCDS-ADRDA criteria [24]. These patients had a baseline MMSE score of 21.3 ± 2.6 [25] and were being treated with acetylcholinesterase inhibitors and/or memantine at a stable dose. Further details of demographic and clinical characteristics of patients have been previously published [23] and summarized for placebo and active treatment groups in Supplemental Table S1.

Treatment groups

Eligible patients were randomly assigned one of the four groups (1:1:1:1), three PE-treated groups and one placebo group. During intensive treatment phase, the three treatment groups received weekly conventional therapeutic PE (TPE) with albumin (Albutein® 5%, Grifols) replacement, through peripheral or central venous access, for 6 weeks. This was followed by a 12-month maintenance period with monthly low-volume PE (LVPE) during which three different treatment modalities were administered: one group received LVPE with low-dose (20 g; 100 mL) 20% albumin (Albutein® 20%, Grifols); one group received low-dose albumin alternated with low-dose (10 g; 200 mL) IVIG (Flebogamma® 5% DIF, Grifols) every 4 months; and one group received high-dose (40 g; 200 mL) 20% albumin alternated with low-dose (20 g; 100 mL) 20% albumin (Albutein® 20%, Grifols) every 4 months. The placebo group received a simulated non-invasive PE (sham) procedure that did not involve any fluid transfer [22, 23]. Placebo patients were subjected to the same procedures and evaluations as PE-treated patients. The patients, caregivers, and neuroimaging evaluators were blinded as to the therapy received.

Image acquisition

MRI and 18FDG-PET measures were taken at baseline (month 0; M0), the intermediate visit after the intensive treatment phase (month 2; M2), month 9 (M9), and the final visit (month 14; M14). MRI scans were also performed at month 6 (M6).

Images were acquired at different imaging sites, MRI with a 1.5 T magnet scanner, and 18F-FDG-PET with PET/CT scanners. Each participating imaging site acquired and reconstructed the data according to a standardized protocol following the Alzheimer’s Disease Neuroimaging Initiative (ADNI) recommendations [26].

MRI acquisition

Patients were asked to lie in supine position, the center of the coil was aligned with the line of the eyes, they were instructed not to move, and the head was gently stabilized with cushions. Whole-brain T1-weighted images of 1-mm isotropic resolution were obtained at isocenter using the magnetization-prepared rapid gradient-echo (MP-RAGE) pulse sequences included in a vendor-supplied package, and using the same acquisition protocol (TR = 2300 ms, TE = 2.98 ms, field of view 256 mm, and 192 sagittal partitions, voxel size = 1 × 1 × 1 mm).

18FDG-PET acquisition

Patients who were claustrophobic or non-cooperative, those without suitable venous access to administer the tracer, and those taking corticosteroids at the time of the test were excluded. Patients fasted for at least 4 h prior to the procedure to provide optimal brain 18FDG uptake that was not influenced by increased blood glucose levels.

Before the injection of 18FDG, blood glucose levels were checked to assure that they were lower than 160 mg/dL. Patients were placed in a quiet, dimly lit room several minutes before 18FDG administration, and during the 18FDG uptake phase (at least 20 min), talking, reading, or listening were avoided. Sedation of patients was not allowed.

A dose of 185 ± 18 MBq (5 ± 0.5 mCi) 18FDG was administered, and 30 min after injection, the images were acquired. Acquisition of CT images was carried out first. Next, 18FDG-PET images were acquired in 3D mode, with an acquisition duration of 15 min, matrix size 128 × 128, slice thickness (Z) of 2.0 mm, and pixel size (X, Y) of 2.0 mm × 2.0 mm. The images were reconstructed with iterative algorithm (15 subsets and 4 iterations).

The images were corrected for attenuation with the CT scan, and were reviewed to assess possible artifacts and movement. Eventually the reconstructed images were reoriented on the orbitomeatal axis.

Individual image analysis

Longitudinal analysis of the 18FDG-PET and MRI scans was limited to patients who completed all study visits and had analyzable scans at all visits.

MRI quantification

FIRST software from the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (Oxford, UK) [27] and SPM8 software (Welcome Trust Centre for Neuroimaging, London, UK) running on MATLAB (MATLAB R2012b, MathWorks, Natick, MA, USA) were used to compute brain volumetry.

FIRST, a fully automated method, was applied to the MPRAGE images to derive subcortical volumes. MRI images were reoriented according to the anatomic FSL atlas, using the fslorient2std tool. Next, the neck region was extracted with the robustfov tool and ran FIRST to determine the volume of the right and left thalamus, putamen, caudate,
the mean and the standard deviation of the distribution. The paired $t$-test implemented in SPM8 was applied considering a statistical threshold of $p < 0.001$ uncorrected and in relation to the unspecific hypometabolic voxels. Those
detected voxels that survive a cluster thresholding using a minimum cluster size of \( k = 50 \) were considered.

SPM maps showing contrasts were superimposed onto a T1 template using MRICron on 12 axial views covering the entire brain. To identify the location of the significant voxels obtained in the SPM analysis, the Wake Forest University (WFU) PickAtlas tool [32] was used.

For each treatment group, the evolution of k-extent (metabolism loss over time (change from baseline)/longitudinal analysis: M2 vs M0; M9 vs M0, and M14 vs M0) was shown in maximal intensity projection (MIP) view. The measurement of defect extent and defect intensity took into consideration all the voxels within the VOI.

The SPM maps showing metabolic decline from M0 to M14 in the placebo group allowed identification of the regions of the brain involved in the natural progression of AD. These data were used to create the Alzheimer’s Disease mask (MaskAD). The MaskAD when applied to the scans of each individual in the treatment groups and allowed the determination of the metabolic defect intensity in the treatment groups compared to placebo.

**Statistics**

Descriptive statistics were calculated for all measured variables (mean, median, standard deviation, 25th percentile, 75th percentile, minimum, and maximum). Comparisons between treatment groups and longitudinal comparisons (M0, M2, M6, M9, and M14) were made using analysis of variance (ANOVA). Pairwise comparisons of different time points within a treatment group were made using Student’s t-test with a significance level set at \( p < 0.05 \). Statistical analyses were performed using SAS software (version 9.2, Cary, NC, USA).

**Results**

**Samples for image processing**

Of the total study population of 322 evaluable patients from AMBAR study, 18FDG-PET scans were missing or unable to be analyzed for 13 patients at baseline (M0). At final visit (M14), 224 images were available. For longitudinal SPM analysis, only patients that completed all study visits and without images unable to be processed could be included leaving 213 patients for 18FDG-PET longitudinal analysis. For MRI, 55 patients had missing or unreadable scans at M0. At M14, 198 images were available. This was the database available for analysis of VOI.

Most patients had both 18FDG-PET and MRI scans available: \( n = 257 \) at M0 (representing 83.2% of 18FDG-PET and 96.3% of MRI), and \( n = 183 \) at M14 (representing 81.7% of 18FDG-PET and 92.4% of MRI).

**Brain volumetry analysis by MRI**

No changes were reported between treatment groups at each cross-sectional time point and in all subcortical and cortical areas and globally there was a loss in volume throughout the 14-month period.

There was a significant volume loss of GM (in absolute values and fraction) in all treatment groups and placebo from M0 to M14. WM in absolute values were not significantly decreased in any treatment group and placebo group, and WM fraction was only reduced in the placebo group, but not in any active treatment groups. On the contrary, significant volume loss of CSF (in absolute values and fraction) was observed in all active treatment groups, but not in the placebo group from baseline to final visit (M14).

When volumetry for subcortical structures was analyzed longitudinally (from M0 to M14), the placebo group showed a significant volumetry loss in 4 areas (hippocampus [L, R] and accumbens [L, R]). For the low albumin group, significant decreases in volume were shown in 9 areas (caudate [L, R], hippocampus [L, R], accumbens [L, R], amygdala [L], putamen [R], and pallidum [R]). The low albumin + IVIG group showed a significant volumetry loss in 8 areas (thalamus-proper [L, R], caudate [L, R], accumbens [L, R], putamen [L, R], and hippocampus [R]). For the high albumin + IVIG, there was a significant volumetry loss in 3 areas: amygdala [L], caudate [R], and accumbens [R]. Therefore, nucleus accumbens [R] was significantly reduced in all treatment groups (active and sham), whereas caudate [R] was significantly reduced in all active treatment groups, but not in placebo group. Pallidum [L] and brain stem 4th ventricle areas were not significantly decreased for all active treatment and placebo groups. All groups except high albumin + IVIG showed a statistically significant reduction of hippocampus [R].

Globally, fewer statistically significant changes in volume were observed over time in the high albumin + IVIG treatment group (\( p < 0.05 \) in 3 structures vs. 4 to 9 in other groups) (Table 1).

**Brain metabolism analysis by 18FDG-PET**

18FDG-PET analyses showed that the baseline defect pattern was consistent with AD (posterior cingulate, both parietal, temporal [slightly more extensive in the left hemisphere], and slight extension to the frontal) and was similar between all treatment groups. Similar defect patterns were obtained for mild and moderate AD patients. No differences were observed in the defect pattern between mild and moderate AD patients or between treatment groups. However, defect
pattern in moderate AD patients was more intense (evidenced by the color of the defect, greener, which means more standard deviations in relation to the normality database) than in mild AD patients, and more extensive (Fig. 1).

Changes in metabolism intensity, defect extension, and defect intensity in all brain areas that had significantly changed between M0 and M14 are shown in Table 2. The high albumin + IVIG treatment group showed the lowest percentage of areas with significant changes in these parameters. Most of the changes in metabolic intensity were seen in the limbic structures, temporal and parietal cortex, and the cerebellum. The primary brain areas

| Placebo | PE-treatment |
|---------|--------------|
|         | Low Albumin | Low Albumin + IVIG | High Albumin + IVIG |
| Accumbens [L, R] | Accumbens [L, R] | Accumbens [L, R] | Accumbens [R] |
| Hippocampus [L, R] | Caudate [L, R] | Hippocampus [R] | Caudate [R] |
| Amygdala [L] | Putamen [L] | Putamen [L] | Thalamus-proper [L, R] |
| Caudate [L, R] | Pallidum [R] | | |
| Hippocampus [L, R] | | | |
| Putamen [R] | | | |
| Total: 4/15 (26.7%) | Total: 9/15 (60%) | Total: 8/15 (53.3%) | Total: 3/15 (20%) |

Fig. 1 Defect pattern in 18F-flurodeoxyglucose positron emission tomography (18FDG-PET) analysis at baseline in Alzheimer’s disease patients treated with plasma exchange with low- or high-dose albumin with or without intravenous immunoglobulin (IVIG). Axial view

Table 2 Change in metabolism intensity, defect extension, and defect intensity in all brain areas (N=116) expressed as a number and percentage of areas that significantly changed (p < 0.05) between baseline and month 14 in Alzheimer’s disease patients treated with plasma exchange (PE) with low- or high-dose albumin with or without intravenous immunoglobulin (IVIG)
affected were the same as those seen when measuring metabolic intensity.

**Parametric analysis of $^{18}$FDG-PET**

The metabolic activity pattern is shown in Fig. 2. The areas that showed maintenance of metabolic activity were the posterior cingulum, precuneus, and parietal cortex extending into the temporal region (Fig. 2A). Analysis of the areas that showed worsening over the study period indicated that the areas affected were the posterior cingulum, precuneus, and parietal and temporal regions of the cortex (Fig. 2B). The high albumin+IVIG treatment group showed the greatest stability over the course of the study.

**Fig. 2** Triangulation view of the metabolic maintenance pattern (A: upper panel) and worsening pattern (B: lower panel) (parametric $^{18}$FDG-PET analysis) over the complete study period (baseline [M0] to month 14 [M14]) in Alzheimer’s disease patients treated with plasma exchange with low- or high-dose albumin with or without intravenous immunoglobulin (IVIG). All patients
The percentage decline in metabolism (MaskAD) from M0 to M14 is shown in Table 3. When all the patient data was considered together, the least amount of decline was seen in the high albumin + IVIG group. By AD severity,

Table 3  Percentage of metabolism loss in MaskAD between baseline and month 14 in Alzheimer’s disease patients treated with plasma exchange (PE) with low or high dose albumin with or without intravenous immunoglobulin (IVIG), stratified by disease severity

| Placebo | PE-treatment |
|---------|--------------|
|         | Low albumin | Low albumin + IVIG | High albumin + IVIG |
| All patients | −4.3 | −3.3 | −3.6 | −2.9 |
| Mild AD | −1.6 | −2.1 | −2.9 | −0.9 |
| Moderate AD | −6.6 | −3.6 | −4.3 | −4.2 |

decline during the study period was less in the mild AD group than in the moderate AD group. High albumin + IVIG had the greatest effect in the mild AD group. In the moderate AD group, the least decline was seen in the low albumin group. Table 3 shows that area of significant metabolic decline was less in the high albumin + IVIG group than in any of the other groups. This was true for the pooled data and when the patients were divided by AD severity. Greater loss of metabolism (increased MaskAD size) was seen in the placebo, low albumin, and low albumin + IVIG groups than in the high albumin + IVIG group. The high albumin + IVIG group showed the smallest MaskAD size in all three brain regions (temporal, parietal, and frontal).

Figure 3 shows the SPM analysis, where there was very little change in metabolism in mild AD patients treated with high albumin + IVIG. Some deterioration was seen in the other three treatment groups. As in the whole patient
population, the effects of high albumin + IVIG were seen consistently across brain regions. There was essentially no change in metabolism in the parietal and frontal lobes over the course of the study in the high albumin + IVIG treatment group while metabolism declined in the other treatment groups.

Table 4 shows that area of significant metabolic decline (size of mask k-extent) in the SPM analysis was smallest in the high albumin + IVIG group. This was true for the pooled data and when the patients were divided by AD severity. Much greater loss of metabolism is reflected in the MIP view from the other treatment groups (Fig. 3).

The effects of treatment were more noticeable in the mild AD patient group. As shown in Supplemental Fig. S1A, at M14 the metabolic intensity decreased while the extension and intensity of defect slightly increased. As with the representative example of moderate AD patients (Supplemental Fig. S1B), the reduction of metabolic intensity at M14 was seen across all cerebral lobes, and more evident the extension and intensity of defect, which doubled.

Discussion

Diagnosis and progression of AD are currently based on clinical observation, scoring on various assessments of cognitive function, and surrogate biochemical markers [33]. Most patients in the AMBAR study, who were enrolled based on the presence of the AD clinical syndrome, had baseline CSF Aβ42 levels ≤600 pg/mL [23]. This is in agreement with patient populations and methods of determination in other studies [23]. However, over the years, there has been increasing interest in the diagnostic utility of neuroimaging. This study explored 18FDG-PET and MRI results from the AMBAR study patients.

Among neuroimaging techniques, computed axial tomography was found to be useful in diagnosing some types of dementia but is of limited usefulness in discriminating AD [34]. Single positron emission computed tomography (SPECT) has also shown some utility in distinguishing some types of dementia [35, 36]. However, 18FDG-PET imaging is a more valuable tool in the assessment of patients with AD [37]. More recently, MRI has demonstrated utility due to a greater capability to distinguish anatomical structures in the brain and provide more precise images [38]. In this study 18FDG-PET and MRI scans performed on AD patients throughout the course of the study were compared with scans performed at baseline (M0) and scans from a population without AD. Moreover, SPM is considered the gold standard for dementia diagnosis [39]. With 213 patients analyzed (49 to 60 per treatment group), this study is one of the largest performed using this technique in a clinical trial.

MRI has been shown to detect structural changes in the brain associated with AD including cerebral atrophy and enlargement of the ventricles and sulci [40, 41]. Our brain volumetry studies showed that the high albumin + IVIG group had fewer structural changes from M0 to M14, including the stabilization of the hippocampus volume. Importantly, the hippocampus plays a key role in developing new memories [42] and is one of the first areas in the brain affected by AD [43].

18FDG-PET analyses of the effects of PE on AD using these scans showed that baseline pattern of defect was consistent with AD [44–47] and similar between all treatment groups. After treatment, metabolic deficits were still seen, but in fewer brain areas and were less extensive in the high albumin + IVIG treatment group than in the other treatment groups or the placebo group. This was particularly evidenced in defect extension and defect intensity, the parameters directly related to neuronal damage rather than metabolic intensity. These effects were observed primarily in the brain regions most affected by AD (posterior cingulate, precuneus and parieto-temporal lobes) [48–50].

When looking at the longitudinal metabolic decline in all brain areas (MaskAD or number of voxels showing a metabolic decline at the end of the study compared to baseline), mild AD patients showed a pattern of metabolic decline over time slower than moderate AD patients, as expected. However, the increase in intensity and extension of defect were not significantly different between any of the treatment groups and placebo. This could be explained by the fact that minimal changes in the high albumin + IVIG group were balanced by the extensive pattern of defect in the two low albumin groups (with or without IVIG), which had change patterns similar to placebo. This suggests that the mild AD patients’ group was more stable over time, regardless of the treatment arm.

Interestingly, the clinical results showed that PE-treated mild AD patients scored better in verbal memory and language fluency tests (particularly in Rey auditory verbal learning test [RAVLT], semantic verbal fluency [SVF], and phonetic verbal fluency PVF) [21]. This paralleled the reduced metabolic deficit observed in the posterior cingulate
gyrus and parietal lobe, where damage is suggestive of AD pathology in patients with language deficits [44, 48]. Moreover, 18FDG uptake in the posterior cingulate-precuneus or in language-related Brodmann areas has been shown to correlate the main indices of RAVLT in patients with mild cognitive impairment (MCI) [51] and in AD [52]. These results are important because PE could stabilize hypometabolism or hypoperfusion in mild AD. These defects are predictors of a rapid progression to more severe AD [53]. More specifically, the angular region, along with the posterior cingulate, are regions that present greater progression of metabolic loss. This finding is in agreement with the findings of Rosselli et al. [54] in which they demonstrated with structural connectivity techniques the integrative role of the angular region in linguistic functions.

In moderate AD patients, there was a significant difference in the extension of defect pattern between high albumin + IVIG and the rest of treatment arms. Low albumin (regardless of IVIG) presented extension defect patterns similar to placebo, whereas high albumin + IVIG group had less loss of metabolism by intensity and extension than the rest. This suggests that the higher dose of albumin was necessary to achieve the neuroprotective effects.

Previously published data from pilot and phase 2 studies showed that the positive clinical effects of PE in AD patients [19, 55] were correlated with positive neuroimaging data [20, 55]. Taking these findings to a further step, dose separation and separate mild-to-moderate AD patients were assessed in this phase 2b/3 study. Clinical results showed that some of the positive cognitive and behavioral effects of PE appeared to be more pronounced in moderate AD patients [23], while memory, language, and processing speed abilities appeared to be more pronounced in mild AD patients [21]. In the present neuroimaging analyses, some positive effects of PE treatment were seen in the mild AD group, while others were seen in the moderate AD group, particularly with high albumin + IVIG.

A potential limitation of this study is that some of the analyses such as metabolism intensity, pattern of defect, and defect intensity are semi-quantitative, which could conceal some of the complexity of AD etiopathology. Additionally, a study period longer than 14 months may be necessary to fully assess whether the treatment has a meaningful impact on the course of AD in these patients. Determining the exact relationship between the effects of PE on brain structure and function (as measured by 18FDG-PET and MRI) and cognitive and behavioral effects will require additional investigation.

In conclusion, PE treatment in AD patients was associated with fewer deleterious changes in selected subcortical structures and less metabolic decline in the specific areas affected in AD than the typical progression of the disease, as observed in the placebo group. These effects were more marked in the group treated with high albumin + IVIG compared to the low albumin groups (with or without IVIG) and in moderate AD patients. Mild AD patients seemed metabolically more stable over time, regardless of the treatment arm.

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Author contribution GC-B was the lead investigator of the imaging branch of the trial. AP was the medical director of the trial and conducted the study oversight as well as provided guidance and expertise on plasma-derived medicines. MBo and OLL were the coordinating investigators of the trial in Spain and the USA, respectively. GC-B, AP, LN, MBo, and OLL were responsible for the design and methods of the trial. MBo participated in patient recruitment and data collection. LN, CG, and MBa were responsible for the trial clinical operations. GC-B, IR, JC-C, and DP contributed to neuroimaging data collection and/or interpretation. MBo, OLL, LN, CG, MBa, and AP contributed to the discussion on Alzheimer’s disease. GC-B, LN, CG, MBa, and AP participated in the manuscript writing up. All authors revised and approved the final version of the manuscript and agreed to the submission.

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Data availability Data reported in this manuscript are available within the article and/or its supplementary materials. Additional data from the AMBAR study (EudraCT#: 2011–001,598-25; ClinicalTrials.gov ID: NCT01561053) are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was conducted in compliance all applicable regulatory guidelines and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), Institutional Review Boards (IRBs) or Ethics Committees from the sites and the Health Authorities from the countries where the study was performed approved the protocol, the informed consent form, and the patient information sheets.

Consent to participate Each patient and caregiver, family member, or legal representative provided informed consent prior to enrollment.

Consent to publish Not applicable.

Competing interests MBo has been a consultant for Araclon, Avid, Bayer, Eli 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-Wyeth, Roche, and Servier. OLL has been a consultant for Grifols and Lundbeck. LN, MBa, CG, and AP are full-time employees of Grifols.
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