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Letter to the Editor

AMBAR: A Therapeutical Approach for Alzheimer's Disease Patients Regardless of Amyloid Status

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Dear Editor,

We read with interest the report recently published by the CTAD Task Force investigators in which the current therapeutic targets for Alzheimer's disease (AD) are approached, with a particular focus on anti-amyloid and anti-tau treatments (1). We acknowledge the relatively limited clinical benefit observed so far in randomized clinical trials (RCT) with therapies targeting various components of the amyloid cascade, beyond the biomarker improvements reported with immunotherapeutic approaches (e.g., aducanumab, lecanemab).

Nevertheless, in our letter we would like to draw attention to the results of the AMBAR (Alzheimer Management By Albumin Replacement) phase 2b/3 RCT, which evaluated plasma exchange (PE) with albumin replacement as an alternative approach to treat mild-to-moderate AD patients. The development strategy of the AMBAR program was initially focused on the amyloid hypothesis, under the rationale that plasmapheresis-mediated removal of patient's plasma containing albumin-bound amyloid beta protein (Aβ), would decrease brain Aβ burden by inducing a shift of free Aβ from cerebrospinal fluid (CSF) to plasma with the aim to delay the clinical progression. Replacement of plasma with therapeutic Aβ-free albumin in a regular PE schedule would thus reinforce the Aβ clearance process. At the same time, beyond effects on Aβ, PE would remove other toxic substances from patient's plasma, including possible pro-aging systemic factors and inflammatory mediators.

In the AMBAR study 322 patients were treated with a 14-month PE program consisting of two periods: six weeks of weekly conventional PE followed by 12 months of monthly low volume PE. There were three PE-treatment modality groups (high or low dose of albumin for plasma replacement, with or without intravenous immunoglobulin to counteract a possible immunological deficit) and one placebo (sham PE) group. Results showed that CSF Aβ42 levels remained stable in the PE-treated patients across the study whereas levels significantly decreased in the placebo group. This suggests that PE might increase clearance of CSF soluble amyloid to prevent its further deposition, which would be consistent with the oberved postive clinical outcome (slowed cognitive and functional decline) (2). Moreover, a bigger effect in the moderate AD stage was observed, while in mild AD patients the patterns of Aβ and tau levels were inconclusive or even counterintuitive. This has led to consider alternative unspecific diverse mechanisms of action that may explain the effect of PE and albumin replacement, which would include mechanisms associated with vascular effects, inflammation, and neurodegeneration, among others. Albumin is postulated to play a key role in explaining such outcomes. Thus, albumin has multiple favorable structural and molecular properties that would confer to this plasma component its numerous pleiotropic physiologic functions (e.g., circulating Aβ-binding capacity. transporter, detoxifier, antioxidant, immunomodulator, anti-inflammatory) (3). In this regard, preliminary results from ongoing investigations performed on samples from AMBAR trial patients have shown both a short and a long term effect of PE with albumin replacement on inflammatory biomarkers such as IFN-γ, eotaxin, MIP-1α and ICAM-1 in serum/plasma, and eotaxin-3 and MIP-1β in CSF (4). Likewise, research on the capacity of PE with albumin replacement to induce changes in proteomic and lipidomic AD patients' profile is in progress.

In addition, in their paper the CTAD Task Force investigators highlight the unmet need of therapies that can be used in patients with an AD-like phenotype, but that are amyloid negative. A key aspect of the AMBAR trial is that eligibility criteria did not consider amyloid status for patient inclusion. Instead, only the phenotypical criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) were applied for the diagnosis of AD (2). Nevertheless, the amyloid status was available in 298 patients (approximately 90% of those randomized). Based on a definition of amyloid positivity of CSF Aβ42/Aβ40 ratio <0.05, approximately 70% of the randomized population was considered

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amyloid-positive and 30% resulted amyloid-negative. Importantly, exploratory analyses demonstrated that the amyloid-negative patients obtained a clinical benefit (i.e., slowing down the decline or stabilization of the disease symptoms) similar to amyloid-positive patients. Hence, there was a statically significant improvement in the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog), Clinical Dementia Rating scale Sum of Boxes (CDR-sb), and Alzheimer's Disease Cooperative, Study-Clinical Global Impression of Change (ADCS-CGIC) tests compared to untreated controls, in the evaluation of scores at month 14 vs baseline (5). These results suggest that PE with albumin replacement may exert a positive therapeutic effect on patients with Alzheimer's phenotype who are amyloid negative. Since multiple mechanisms appear to be involved in AD pathogenesis, this would be in agreement with the CTAD Task Force investigators' demand of a further discussion beyond exclusion of this specific AD population from antiamyloid RCTs. Further investigation of the role of PE with albumin replacement in phenotypic AD patients is warranted to confirm these findings.

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