The Journal of Prevention of Alzheimer's Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Editorial

Astrocytes provide a unique biomarker for Alzheimer's and other pathologies

In an article published in this issue of the Journal of Prevention of Alzheimer's Disease (JPAD) [1], Abbas and Ferreira et al. provide important new insights into the use of plasma glial fibrillary acidic protein (GFAP) in clinical trials of Alzheimer's disease (AD). Plasma GFAP has been used as a proxy of astrocyte reactivity, which is known to be changed along with other pathologies associated with AD [2]. As noted by the authors, blood-based biomarkers may have distinct advantages over positron emission tomography (PET) biomarkers and even cerebrospinal fluid (CSF) biomarkers. Biomarkers for AD have focused primarily on amyloid plaque load (assessed by amyloid PET, CSF Aβ42/Aβ40 ratio, and more recently plasma Aβ42/Aβ40 ratio), neurofibrillary tau tangles or various species of phospho-tau (as assessed by PET, CSF or more recently plasma), and to an increasing extent by GFAP measured in plasma. By combining data from three longitudinal observational studies [Translational Biomarkers in Aging and Dementia (TRIAD), Alzheimer's Disease Neuroimaging Initiative (ADNI), and Biobank Innovations for Chronic Cerebrovascular Disease with Alzheimer's Disease Study (BICWALZS)], the authors have provided data supporting a unique role of plasma GFAP in AD clinical trials.

The authors categorized participants into four groups: clinically unimpaired (CU) and amyloid negative, clinically unimpaired and amyloid positive (i.e. preclinical AD), clinically impaired (CI) and amyloid negative, and clinically impaired and amyloid positive (i.e. AD). Based on change from baseline to endpoint, interestingly the CI but amyloid negative population did appear to show changes from baseline in GFAP. The only group not showing changes from baseline in GFAP was the CU/amyloid negative population, although trends were seen in the data. Importantly, powering analyses for each of these groups was provided, and not unexpectedly powering for a CU/amyloid negative population was substantially limited.

The manuscript makes several references to the use of plasma GFAP as a secondary outcome measure for clinical trials. From a regulatory standpoint, secondary outcomes can be an important consideration, but they generally must be evaluated with controls for multiple comparisons using a variety of statistical techniques, especially when part of a pivotal registration trial. Positive secondary outcomes with appropriate statistical analyses can be considered for inclusion in labelling. Historically, regulatory agencies have not required biomarker analyses to be corrected for multiple comparisons, and thus they might not be considered a secondary outcome, but with an increasing understanding of various biomarkers for AD, the regulatory position on this issue could change. How any biomarker could be considered as a secondary outcome is an important topic and is likely to evolve over time. In non-registration Phase 2 trials used only for making go/no-go decisions for further development, a sponsor may use biomarkers or other outcomes as secondary or even primary outcomes as they deem appropriate.

From a biological perspective, the addition of GFAP to the biomarker armamentarium for AD is likely to be important. While amyloid plaque deposition is broadly accepted as leading to changes in various phospho-tau species and tau tangles, changes in an astrocytic marker such as GFAP brings another aspect to assessing AD pathology [3]. The powering estimates provided in this publication are related to 18-month trials with GFAP as a secondary outcome. Changes in GFAP in clinical trials could also be included in early phase AD trials as a demonstration of central pharmacology, since recent data have suggested that changes in plasma GFAP could be demonstrated with a disease-modifying drug in a period of just weeks to months [4].

The specificity for GFAP, especially with regard to vascular disease, is also discussed by the authors and is an important topic. The fact that GFAP may be increased in other causes of dementia, perhaps mostly vascular, is acknowledged by the authors, but that fact may not diminish its relevance for AD studies. Given that virtually all AD trials now require confirmation of AD pathology based on amyloid deposition, changes in GFAP in other disease states, e.g. vascular dementia, are of relatively limited concern in studies of patients with AD when the diagnosis is confirmed by other AD biomarkers.

Declaration of generative AI and AI-assisted technologies in the writing process

AI was not used in the writing of this manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Eric Siemers reports a relationship with Acumen Pharmaceuticals Inc that includes: employment and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DOI of original article: 10.1016/j.tjpad.2025.100205

https://doi.org/10.1016/j.tjpad.2025.100233
Received 2 June 2025; Accepted 10 June 2025
Available online xxx

CRediT authorship contribution statement

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References

[1] Abbas S, et al. Utility of plasma GFAP as a secondary endpoint for clinical trials in Alzheimer's disease. J Prev Alzheimers Dis 2025. doi:10.1016/j.tjpad.2025.100205.
[2] Sanchez-Juan P, et al. Serum GFAP levels correlate with astrocyte reactivity, post–mortem brain atrophy and neurofibrillary tangles. Brain 2024;147(5):1667–79.
[3] Chatterjee P, et al. Plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL across the Alzheimer's disease continuum: a cross-sectional and longitudinal study in the AIBL cohort. Alzheimer's & Dementia 2022.
[4] Cline EN, et al. Biofluid biomarker changes following treatment with sabirnetug (ACU193) in INTERCEPT-AD, a phase 1 trial in early Alzheimer's disease. J Prev Alzheimers Dis 2025:100082.