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Letter to the Editor

Long-term treatment of early Alzheimer's disease with donanemab

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Dear Editor,

We read with great interest the article by Zimmer and colleagues reporting the 36-month long-term extension of the TRAILBLAZER-ALZ 2 study, recently published in *The Journal of Prevention of Alzheimer's Disease* [1]. The authors should be commended for providing much-needed longer-term data on donanemab, including sustained amyloid plaque clearance, maintenance of clinical benefit after treatment discontinuation, and a safety profile that appears broadly consistent with that observed during the parent trial.

Despite these encouraging results, several unresolved issues warrant careful consideration. First, the population eligible for donanemab treatment remains numerically very small when compared with the overall number of patients with early Alzheimer's disease (AD). Stringent inclusion criteria, particularly amyloid and tau biomarker requirements, *APOE ε4*-related safety concerns, and exclusion of patients with significant cerebrovascular comorbidity, raise the question of whether this highly selected subgroup can realistically represent the main target population for national health systems. This concern is especially relevant given the high direct and indirect costs associated with biomarker screening, infusion-based administration, MRI monitoring, and management of adverse events.

Second, although the long-term extension confirms a favorable benefit-risk balance in trial conditions, the risk of amyloid-related imaging abnormalities (ARIA), including cerebral edema, micro- and macro-hemorrhages, stroke-like symptoms, and rare fatal outcomes, remains clinically meaningful [2,3]. These safety issues, together with controversial interpretations of clinical effect sizes, have fueled ongoing debate regarding the real-world value, affordability, and equitable allocation of anti-amyloid monoclonal antibodies across different healthcare systems [4].

In this context, it is important to revisit the assumptions underlying the definition of a clinically meaningful disease-modifying effect. It has been proposed, somewhat arbitrarily, that a slowing of clinical decline by at least 25% per year constitutes an acceptable threshold for disease modification, corresponding to a delay of approximately three months per year in symptom progression [5]. Using this framework, early-start donanemab treatment in TRAILBLAZER-ALZ 2 was estimated to save about 6.9 months over three years on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) compared with an external ADNI cohort, while delayed-start treatment saved approximately 5.6 months on CDR-SB progression at the end of the long-term extension, about 18 months after treatment initiation [1].

However, interpretation of these findings is complicated by reliance on published summary statistics rather than individual-level data, differences in trial populations and designs, and the inherent uncertainty of cross-study comparisons. When the same "time-saved" approach is applied to non-pharmacological interventions, such as the multinutrient medical food Souvenaid™, long-term treatment has been estimated to save approximately 16 months on CDR-SB progression at three years in patients with early AD [6,7]. Although such comparisons must be interpreted with caution, they highlight the need to abandon the implicit assumption that non-pharmacological evidence should be viewed with greater skepticism or relegated to a secondary role.

Taken together, these considerations suggest that donanemab represents an important and innovative therapeutic option for a subset of patients with early AD, but not a definitive or universally applicable solution. Efforts to simplify administration, reduce monitoring burden and costs, and initiate treatment earlier in the biological continuum of the disease may enhance its overall value. At the same time, greater integration of pharmacological and non-pharmacological strategies, grounded in clinically meaningful outcomes such as functional independence and quality of life, may offer a more sustainable and equitable approach to disease modification in AD.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

The authors declare that they did not use any generative AI and/or AI-assisted technologies in writing the manuscript TJPAD-26–00,085.

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Vincenzo Solfrizzi: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Bruno P. Imbimbo:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

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