J Prev Alz Dis 2022;9(S1):S5-S6
Published online December 3, 2022, http://dx.doi.org/10.14283/jpad.2022.95

Editorial

We Have Turned the Corner

P.S. Aisen[1], B. Vellas[2]

1. Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; 2. Toulouse Gerontopole University Hospital, Universite Paul Sabatier, INSERM U 1295, Toulouse, France

Corresponding Author: Paul S. Aisen, Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA, paisen@usc.edu

Key words: Alzheimer, drug, clinical trials, Alzheimer therapy.

The decades-long effort to develop disease-slowing therapy for Alzheimer's disease has been littered with failure and frustration. Academic investigators have debated the reasons, reaching starkly different conclusions. Some companies have abandoned their efforts. Most of the clinical trials have focused on targeting amyloid. The rationale has been compelling, but the number of negative trials has led many to urge abandoning the strategy.

Contentious debate peaked over the aducanumab development program. Aducanumab was the first anti-amyloid monoclonal antibody to demonstrate substantial reduction in brain fibrillar amyloid associated with apparent slowing of clinical progression (1). But the Phase 3 program was interrupted based on a flawed interim futility analysis, yielding two incomplete datasets with conflicting results (2). U.S. Food and Drug Administration (FDA) reviewers drew different conclusions about the overall submission, while the external advisory committee voted against approval. The final FDA decision was accelerated approval based on the view that amyloid reduction, clearly demonstrated in both pivotal trials, was reasonably likely to predict clinically meaningful benefit; this conclusion was supported by Phase 2 trial data for two other amyloid-lowering antibodies, lecanemab and donanemab (3). The accelerated approval required an additional study post-marketing that supported a clinical benefit.

Debate raged on in the field and in the media, with many urging that AD drug development efforts be re-directed to other therapeutic strategies. The U.S. Centers for Medicare & Medicaid Services (CMS) decided that apart from approved trials aducanumab therapy would not be reimbursed. The sponsor discontinued marketing aducanumab while pursuing the follow-up study mandated by the FDA.

Now the topline results of the Phase 3 lecanemab trial in early symptomatic AD have been released. This completed large international study met its primary endpoint: lecanemab treatment of individuals with early AD slowed by 27% clinical progression as measured by change in the Clinical Rating Scale Sum-of-Boxes (CDR-SB) score at 18 months. All key secondary outcomes were also positive, confirming a slowing of progression on cognitive and functional scales. Lecanemab is now on the path to a full approval in the U.S. and elsewhere, the first for a disease-slowing therapy for AD. We have achieved a major milestone.

In contrast, topline results just released indicate that the Phase 3 gantenerumab studies missed their primary endpoint, showing only minimal, non-significant slowing of clinical decline and lower than expected reduction in brain amyloid. These disappointing results may be related to subcutaneous rather than intravenous administration and/or the long dose titration period in these studies.

Controversy will continue. How important is the 27% slowing of progression seen with lecanemab? What is the clinical importance of a treatment effect of less than one half of a point on an 18 point scale? Arguments supporting the importance of the beneficial effect point to the face-validity of the CDR-SB as a measure of clinically meaningful benefit (even at a magnitude of one half point), the likelihood of increasing benefit with continued therapy and the substantial delay to feared events such as loss of independence that may be anticipated. Ongoing consideration of this issue should contribute to the development of improved measures of clinically meaningful benefit for future trials.

The more important question concerns our best path to building on this success and enlarging the clinical benefit. We will soon learn the results of other amyloid-reducing antibodies in similar early AD populations, potentially presenting new options. Perhaps earlier intervention, at the pre-symptomatic stage of disease before the accumulation of irreversible neurodegeneration, will yield more dramatic benefits. This reasonable hypothesis is now being tested in trials of lecanemab, donanemab and gantenerumab that are still years from completion.

For greater benefit in symptomatic AD, a combination therapy approach may be required. Other strategies abound, from anti-tau therapies to neuroprotective, vascular, anti-inflammatory, and neuroendocrine approaches, though none yet has yielded convincing evidence of clinical benefit. Adding on to amyloid reduction may improve the likelihood of success of alternative strategies. We must continue to rigorously pursue the most plausible approaches. Rapid progress will require collaboration and sharing of data and

Received October 17, 2022
Accepted for publication November 14, 2022

methodologies, and the generous participation of representative populations in our trials. The success of lecanemab in early AD may complicate future trial designs, but should invigorate worldwide efforts to continue the advance toward disease control. Advances in trial methodology, particularly the development of accurate plasma biomarkers of AD neuropathology, will accelerate further progress. The outlook for effective interventions against the neurobiology of AD is bright indeed.

Conflict of interest: PSA has received research support from Biogen, Eli Lilly, Janssen, Eisai, the Alzheimer's Association, the National Institutes of Health, and the Foundation for the National Institutes of Health; he has consulted for Merck, Roche and ImmunoBrain Checkpoint. BV is an investigator in clinical trials sponsored by Biogen, Lilly, Roche, Eisai Pharmaceuticals, and the Toulouse University Hospital (Inspire Geroscience Program). He has served as SAB member for Biogen, Alzheon, Green Valey, Norvo Nordisk, Longeveron, but received no personal compensation. He has served as consultant and/or SAB member for Roche, Lilly, Eisai, TauX , Cerecin with personal compensation.

References

1. P. Chiao, B.J. Bedell, et al. Impact of Reference and Target Region Selection on Amyloid PET SUV Ratios in the Phase 1b PRIME Study of Aducanumab Journal of Nuclear Medicine January 2019, 60(1)100-106; DOI: https://doi.org/10.2967/jnumed.118.209130
2. S. Budd Haeberlein, P.S. Aisen, F. Barkhof, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis 2022;9(2):197-210. doi: 10.14283/jpad.2022.30.
3. J. Cummings, G. Lee, P. Nahed, et al. Alzheimer's disease drug development pipeline: 2022.Alzheimers Dement (NY). 2022 May 4;8(1):e12295. doi: 10.1002/trc2.12295. eCollection 2022

How to cite this article: P.S. Aisen, B. Vellas. Editorial: We Have Turned the Corner. J Prev Alz Dis 2022;9(S1):S5-S6; http://dx.doi.org/10.14283/jpad.2022.95