J Prev Alz Dis 2022;9(S1):S3-S4
Published online December 3, 2022, http://dx.doi.org/10.14283/jpad.2022.94

Editorial

Current Themes and Controversies in the Alzheimer's Disease Field: Looking Ahead to the CTAD Meeting in San Francisco, November 29-December 2 2022

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

After reviewing all the abstracts and final program for the upcoming CTAD meeting, several major themes have emerged.

Phase 3 trials of disease modifying monoclonal antibodies (mAbs) against amyloid plaques

During the 23 years since Dale Schenk demonstrated that injection of amyloid beta into mice generated anti-amyloid antibodies which removed amyloid plaques (1), there have been many efforts to demonstrate the effectiveness of this approach in humans. There have been numerous negative trials, often associated with serious adverse effects, leading many to say that this approach is doomed to failure and that the "amyloid hypothesis" (2) has little merit. The experience with Biogen's Aducanumab (Aduhelm), a mAb that significantly lowered amyloid plaques in humans (3) was mixed for several reasons. First, they halted their two Phase 3 trials early (apparently because of futility) only then to show that one (but not both) of the trials demonstrated significant slowing of progression. Additionally there were significant side effects, mostly ARIA. Second, the FDA advisory panel strongly recommended not to approve Aducanumab, but the FDA granted accelerated approval based on amyloid plaque removal. Finally, the Center for Medicare Services (CMS) declined to reimburse for Aduhelm, leading to extremely little clinical use.

Then, a press release from Eisai last month reported that their single Phase 3 study of Lecanemab, another plaque clearing mAb, met its primary and secondary endpoints, with a significant 27% slowing of the decline in CDR sum of boxes. We have few details of this study, but Eisai is scheduled to present at CTAD and we eagerly await the data. Furthermore, Roche has completed its Phase 3 study of Gantenerumab, and they have informed the CTAD that they also wish to present their results. As of this writing these have not been announced. The Eisai and Roche presentations alone will make this CTAD meeting very informative and exciting. There will be panel discussions of the data, and there will be opportunities for panelists and speakers from the audience to voice their enthusiasm, questions, and concerns about these studies. There are some (including myself) who believe that the cognitive decline associated with plaque clearing mAbs has clinical significance and affirms the amyloid hypothesis, but others disagree and all voices will be heard.

Other clinical trial results

In addition to the above, the CTAD program is rich with results of Phase 1 to Phase 3 clinical trials of all types of therapies including mAbs and small molecules, as well as risk reduction studies. Some of these will be platform presentations and there will be many outstanding poster presentations as well.

Biomarkers, especially plasma biomarkers

Twenty years ago, the major biomarkers used in AD research were MRI (to measure brain atrophy), FDG PET (to measure brain metabolism), and amyloid/tau analysis of cerebrospinal fluid from lumbar punctures. Chet Mathis's invention of the amyloid PET tracer, 11C-Pittsburgh compound B, revolutionized our diagnostic approach, because this facilitated diagnosis of amyloid plaques in life. Subsequently, fluorinated PET tracers made by several manufacturers have allowed widespread distribution of both amyloid and tau PET tracers. These tracers are currently widely used in many clinical trials, but they are not reimbursed by Medicare in the USA, and thus they have had little practical impact on clinical practice. The demonstration that plasma assays can detect a lowering of the $A\beta_{42}/A\beta_{40}$ ratio (4, 5) launched the era of plasma testing. Shortly thereafter it was shown that plasma ptau181 is elevated in AD

Received October 18, 2022
Accepted for publication October 19, 2022

(6). More recently ptau217 appears to have even better diagnostic performance (7). Many academic laboratories, diagnostic companies and pharmaceutical companies have been exploring the use of both immune- and mass spectroscopy-based assays. Thus far, almost all studies have been "retrospective studies" using batches of plasma samples banked from participants who had amyloid PET scans and clinical evaluations in the past. Most of the cut points have been derived from the batch samples and the AUC values presented are from the same batch, which is not ideal. Some comparison studies of different methods have been published (8, 9) and more of these are needed. What is needed is for validation data to be obtained where cut points are first determined and then applied prospectively to samples which are analyzed over time. Some prospective studies of this type will be presented at CTAD. We expect that plasma assays will come into the clinic (10). In addition, the plasma biomarkers have been shown to change after mAb treatment removes amyloid plaques. More data concerning the therapeutic effects on biomarkers will be shown at CTAD.

CTAD is unique in our field in that there is only one platform presentation at a time, resulting in a very limited number of oral platform presentations over the three day meeting, We expect that all these talks will be extremely interesting and high quality. This year we had a record number of submissions, and many deserving abstracts which would be platform presentations at other meetings with simultaneous sessions will be posters at CTAD. We strongly encourage a tour of the poster sessions.

This is a beautiful time of the year in San Francisco. Due to our drought, we pray for rain but it is not expected. There are many wonderful places to see, great restaurants, and great beauty. We look forward to seeing you in San Francisco at the Hilton for CTAD this year.

Conflicts of interest: Dr. Weiner received funding from NIH grant U19-AG024904. He has consulted for Cerecin, BioClinica, Nestlé, and Roche/Genentech, and received honoraria from the Buck Institute for Research on Aging, and China Association for Alzheimer's disease. He has patents at the University of Southern California, NerveGen, and CTAD Congress. He has served on the Internal Review Board of the University of California San Francisco and the Roche Advisory Board, and owns stock in Anven, Alzecal, and Alzheon.

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How to cite this article: M.W. Weiner. Editorial: Current Themes and Controversies in the Alzheimer's Disease Field: Looking Ahead to the CTAD Meeting in San Francisco, November 29-December 2, 2022. J Prev Alz Dis 2022;9(S1):S3-S4; http://dx.doi.org/10.14283/jpad.2022.94