J Prev Alz Dis 2022;2(9):188-189
Published online April 5, 2022, http://dx.doi.org/10.14283/jpad.2022.35

Editorial

Where Do We Go from Here?

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Budd Haeberlein and colleagues presented the data from the two randomized Phase 3 studies of aducanumab in early Alzheimer's disease (AD) recently in JPAD (1). The data have been carefully evaluated by the field over the past few years and are now finally reported for closer scrutiny. Essentially, the two studies involved 3,285 participants with mild cognitive impairment or mild dementia due to underlying AD as documented by amyloid positivity. One study, EMERGE, demonstrated statistically significant findings on the primary outcome measure, three secondary measures and a tertiary measure. The parallel study, ENGAGE, failed to replicate these results. The sponsor did post hoc analyses on the ENGAGE study to rationalize its failure to replicate the EMERGE results and suggested several plausible hypotheses. Central to this discussion was the implementation of protocol amendments during the conduct of the study that may have differentially influenced the outcomes of the two studies. The studies were stopped for futility in March of 2019 according to predetermined guidelines. The sponsor, however, evaluated an expanded dataset beyond the data available to the iDMC and concluded that EMERGE demonstrated positive results while ENGAGE did not.

The socio-political fallout of these studies has been enormous. From the original termination of the studies due to futility through the subsequent analyses of additional double-blinded data, the FDA's willingness to entertain a filing, the FDA Advisory Committee's recommendations, the accelerated approval by the FDA on June 7, 2021, and the subsequent consideration for coverage by CMS have resulted in a firestorm. As such, it may be time to step back from the media circus and look at the implications of these studies for the field and, most importantly, our patients.

An interpretation of these data could conclude that there is a positive effect of aducanumab on clinical progression of AD, but the effect is modest. The combination of the positive results from the EMERGE study would be statistically quite unlikely to have happened by chance. However, these data need to be interpreted in the context of the negative results from the parallel study, ENGAGE. This may reflect reality. The impact of intervention on amyloid at the stage of plaque development, along with the symptoms of mild cognitive impairment or mild dementia, may be minimal. If one accepts the putative explanation of the development of AD pathophysiology with amyloid accumulation occurring over years to decades subsequently leading to tau hyperphosphorylation, synaptic dysfunction and cognitive impairment, then results of these types of amyloid interventions may be comprehensible. That is, if amyloid has built up over decades and if one is able to successfully reduce the plaque burden over the course of 12 to 18 months, what might be a reasonable clinical manifestation of that intervention? One could argue that the expectations should be quite modest but perhaps clinically real. The other monoclonal antibodies against amyloid that lower amyloid plaque levels currently under investigation are reporting congruent results of similar magnitude supporting the aducanumab data (2-4). As such, amyloid reduction at the plaque-formation stage might only be expected to have a minimal clinical impact.

The EMERGE and ENGAGE studies suggest a positive effect on downstream biomarkers of the AD pathophysiologic cascade evidenced by tau PET, cerebrospinal fluid markers and plasma p-Tau181 measures. However, as the authors admit, these data are only suggestive due to the small number of participants involved in these substudies. Although the p-tau181 numbers were reasonable, this biomarker is least well validated in clinical trials. The only reliable biomarker data that resulted from this study involved the dose- and time-dependent amyloid-lowering plaque measure obtained on amyloid PET. The other markers are certainly suggestive but hardly definitive regarding substantiation of the ultimate beneficial effect of aducanumab on lowering amyloid levels.

The side effect profile of aducanumab is real and probably reflective of this class of therapies. The incidence of ARIA is significant but perhaps manageable with appropriate monitoring of the development of the ARIA-E and ARIA-H side effects (5). Subsequent data have suggested that these side effects, while real and potentially serious, can be managed and, in the appropriate setting, will allow the continuation of the therapy in most patients (6).

I must take issue with the authors' suggestion that the futility analysis was suspect. The iDMC made the correct decision given the data with which they were presented

Received March 28, 2022
Accepted for publication March 30, 2022

on December 26, 2018, and the constraints under which they were operating. The authors acknowledge "The prespecified futility criteria were met." However, after looking at three months of additional data regarding the continuation of EMERGE and ENGAGE studies beyond the data made available to the iDMC, the authors concluded that two of the futility criteria were not met: 1) the treatment effect of the two studies would be similar and 2) constancy of effect. As such, with the hindsight of the additional data, the authors concluded that two of the assumptions for the futility analysis were violated. While EMERGE and ENGAGE were designed to be identical, they were not conducted in an identical fashion, and consequently, this may have contributed to the discrepant results between the two studies. However, these reflections only became apparent months after the iDMC performed its analysis. If one were to reflect on the design of the futility analysis, one could conclude that the studies should not have been pooled. But again, that is 20/20 hindsight.

What now?

At the end of the day, I think it is incumbent upon us to view these data from the perspective of the patient. The combined data from EMERGE and ENGAGE suggest a modest clinical benefit, but this must be interpreted in the broader clinical context of a fatal disease. Additional data from ongoing studies involving donanemab, lecanemab, and gantenerumab suggest a modest effect of intervention on amyloid with this class of monoclonal antibodies (2-4). In reality, as discussed above, given the duration of the accumulation of amyloid over many years and the reduction of the plaque level in a relatively short period of time, substantial clinical benefits of this type of intervention may not be expected over the course of an 18-month study. It may take years for the benefit of an amyloid-lowering therapy to become manifest. Of course, there is always the argument that earlier intervention may be more beneficial than intervention on amyloid at the symptomatic stage of the disease. Several preclinical anti-amyloid trials are underway (7).

It is most likely that an intervention on amyloid is only a partial attempt at treating a complex disease like AD. It is more probable that amyloid therapies, perhaps very early in the pathophysiologic course, coupled with other therapeutic interventions such as anti-tau therapies and interventions on other neuropathological entities that are frequently present, such as alpha-synuclein, TDP-43, vascular disease, and CSF dynamics, will be necessary. In this context, the intervention on a single pathological process, such as amyloid, may be real and important, but only partially effective in producing a significant clinical impact on our patients. The data from EMERGE and ENGAGE are complicated, and the political fallout surrounding these studies has been unfortunate. We need to see the outcomes of the other monoclonal antibodies against amyloid to put the aducanumab data in perspective. It is hoped that the data from the monoclonal antibody trials will open the door for disease-modifying therapies for our patients. Ultimately, our patients need to be involved in the decision-making process regarding implementation of these therapies (8).

Conflict of interest: Dr. Petersen consults for Roche, Inc., Merck, Inc.; Biogen, Inc.; Eisai, Inc.; and Nestle, Inc. He served on a DSMB for Genentech and receives royalties from Oxford University Press and UpToDate.

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How to cite this article: R.C. Petersen. Where Do We Go from Here?. J Prev Alz Dis 2022;1(9):188-189; http://dx.doi.org/10.14283/jpad.2022.35