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POLICY FORUM

ENGAGE and EMERGE: Truth and consequences?

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Abstract

The potential benefit of the anti-amyloid drug aducanumab based on results of recent EMERGE and ENGAGE clinical trials has generated great controversy and has very important implications for the future of anti-amyloid drug therapies. The two trials of 18-month duration were done in patients with mild cognitive impairment (MCI) and early dementia. The ENGAGE trial showed no benefit while the high-dose EMERGE trial initially also showed no benefit but with longer follow-up there was a significant positive benefit. A recent review form the U.S. Food and Drug Administration (FDA) Advisory Committee was negative while the FDA Office of Neurological Drugs was positive and the statisticians negative. This has generated debate about whether the drug should be approved, disapproved, require a new clinical trial, or approved for a subsample only. The implications for treating both MCI and Alzheimer's disease (AD) patients with anti-amyloid drugs is very substantial as well as the brain amyloid-AD-dementia hypothesis.

KEYWORDS
aducanumab, Alzheimer's disease, amyloid, clinical trials, dementia, Food and Drug Administration

The recent decision by a U.S. Food and Drug Administration (FDA) Advisory Committee of the lack of benefit of aducanumab based on the results of the ENGAGE and EMERGE trials, that is, 301 and 302, is very worrisome for the Alzheimer's disease (AD) research community and, most important, for a large number of patients with mild cognitive impairment (MCI) and early AD.[1,2]

The two trials were practically identical in their design and had an 18-month duration among patients mean age of 70 with MCI and early AD. The primary outcomes were the effect of the drug on the Clinical Dementia Rating (CDR) Sum of Boxes with several other cognitive and behavioral secondary outcomes. The effect of aducanumab on changes in cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers was examined in a subsample.[1]

The ENGAGE trial showed no benefit of drug therapy versus placebo, both at low and high dose, while the EMERGE trial showed statistically significant benefit with a higher dose. However, the EMERGE trial had initially been stopped because of apparent futility, that after further data with longer follow-up showed a positive benefit in the high-dose (10 mg) group. This would be the first trial that was statistically significant in showing an effect of I an anti-amyloid drug on progression of cognitive and physical decline in patients with MCI and early AD.

The subjects in the EMERGE trial had been unblinded after the futility decision but after the FDA review showed that the positive effects of the drug were already apparent before the unblinding.[1] The drug company, in partial collaboration with the FDA, did extensive subgroup analysis to try and explain why one of the two trials was positive and the other had no effect.[1] Two possible explanations were provided: (1) there were more outliers, individuals who had a rapid decline in the ENGAGE than in the EMERGE trial, and removal of these outliers made the results of the two studies more compatible in showing the positive effect; and (2) that a smaller number of participants in the ENGAGE trial had received the higher doses of the drug therapy. The FDA Office of Neurological Drugs was positive to consider the potential benefits of the drug. The Alzheimer's Association (AA) wrote a supporting letter to the FDA prior to the Advisory Committee review supporting the

positive results based on the EMERGE trial but also urged a new Phase 3 outcome trial.[3]

The statistical review at the FDA was negative, including their view that the EMERGE trial was also negative and recommended disapproval of the application to the FDA.[1] Much of their questioning related to the associations between the clinical results and the biomarkers, the characteristics of the subjects, and subgroup analyses. Knopman and colleagues suggested that the apparent benefit in the ENGAGE trail after analyzing primarily the high dose was due to a change in the placebo group between the two. The change in the placebo group went from 1.55 increase in the total sample to 1.79 in the sample that included only those who had high doses for 14 weeks. However, the article was based on a very small sample size; only 26% of the 340 in the placebo were counted in that secondary analysis and no confidence limits around those point estimates were provided. Furthermore, the FDA clinical reviewer provided with more data noted that the benefits after including only the high-dose participants was not due to changes in the placebo. Finally, Knopman and colleagues suggested a new Phase 3 trial prior to approval of the drug, probably at least another 4 or 5 years.[4,5]

A Letter to the Editor in *Lancet Neurology* suggested that the benefit, if any, of aducanumab was very small and may be of little clinical importance for reducing disability among MCI patients.[5]

One group then further questioned whether the AA had received funding from Biogen drug company and support influenced their decision about the benefit of the trial. Nevertheless, the FDA Advisory Committee voted overwhelmingly against the drug.[6]

There are no pharmacological therapies to prevent or to delay the development of AD in spite of the fact that longitudinal studies report a strong relationship between the amount of amyloid in the brain and the incidence of dementia as well as genetic studies demonstrating that increased amyloid production is associated with substantial increased risk of premature AD.[7–9] Indeed, there is solid evidence in the ENGAGE and EMERGE trials that aducanumab reduced the amount of brain amyloid.

There are several reasons why we have not seen greater benefits from anti-amyloid drugs. First, the drugs may not be as effective in reducing the type or amount of amyloid that is associated with cognitive decline and dementia. This is similar to the early experience with drugs for lowering blood cholesterol level, such as clofibrate, which lowered total cholesterol but had little effect on clinical coronary artery disease and increased total mortality.[10]

A second basic problem is that the trials are very expensive, difficult to do, and therefore are of short duration; that is, ENGAGE and EMERGE were 18-month trials with many participants not reaching the 18-month endpoint. The incubation period from MCI to dementia may be longer than the length of the trial. In the Cardiovascular Health Study Cognition Study, the time from incident MCI to incident dementia was about 3 years.[11] Unpublished data from the Ginkgo Evaluation of Memory Study also showed a 3-year time to dementia and in participants with higher amyloid load having shorter duration to dementia.[11] The early converters that will be identified within the first 18 months may have more significant neuropathology secondary to the amyloid and neurodegeneration, loss of synapses, or associated substantial vascular disease and therefore are less likely to benefit from aducanumab. The results of the EMERGE trial with a shorter follow-up was associated with no effect and a futility decision that recommended stopping the study is consistent with the fact that these trials may need longer follow-up for more of the participants as well as higher doses. Small brain hemorrhages, amyloid-related imaging abnormalities (ARIA) have led to reduction of dose of the anti-amyloid drug therapies.[1]

A third possibility is that these trials are being done too late in the natural history of the disease. The ongoing A4 trial is testing an anti-amyloid therapy in individuals who are "cognitively normal" but have abnormal brain amyloid deposition.[12]

A fourth issue is that the design of these trials is faulted. Many of these trials, both ENGAGE and EMERGE, are done in numerous centers in different countries with numerous clinical evaluators even though the evaluators are often not members of the team doing the study, so as to avoid bias. There is a high percentage of participants with incomplete long-term follow-up necessary to evaluate the endpoints. The heterogeneity of the study populations may also be a problem in evaluating the results of the trials. The participants in the trials have prevalent clinical disease, that is, MCI, early dementia, and are likely selective for slower progression from MCI to dementia and death.

We are at a critical turning point in the evaluation of anti-amyloid drugs. If after the results of the ENGAGE and EMERGE trials these drugs are not approved, and another large and expensive trial may not be done, then we are dependent primarily on the A4 trial for the evaluation of anti-amyloid drugs only for individuals as a preventative therapy.[12] What would happen if the A4 trial were negative after we

RESEARCH IN CONTEXT

1. **Systematic review**: Previous trials of anti-amyloid drugs have not consistently shown a reduction in the progression of mild cognitive impairment (MCI) or Alzheimer's dementia. The aducanumab trials, ENGAGE and EMERGE, among patients with MCI or early Alzheimer's disease (AD) have reported conflicting results.
2. **Interpretation**: The U.S. Food and Drug Administration (FDA) Advisory Committee recently voted against approval of the drug. The FDA Office of Neurological Drugs was more positive and the statistical group, quite negative.
3. **Future directions**: The continued controversy about the risks and benefits of aducanumab has important implications for the future of other anti-amyloid drugs and interpretation of the amyloid—AD–dementia hypotheses and especially the health of patients with MCI and early dementia.

have decided that the results of the ENGAGE and EMERGE trials are also negative? Then, do we abandon anti-amyloid drug therapy and the amyloid hypothesis?

We suggest the following:

- Continue the long-term follow-up of the EMERGE and ENGAGE trials and try to follow all the participants and determine endpoints for the participants in relationship to AD, dementia, mortality, and morbidity. The same or similar instruments should be used in the follow-up to measure the effects on cognition and function. This would provide very useful information on the long-term trends of the drug therapy and whether the apparent benefit in ENGAGE in the high-dose group persist or even gets larger.
- Allow the use of aducanumab in a limited protocol to patients with MCI or early AD only at National Institute on Aging (NIA)-supported Alzheimer's Disease Research Centers (ADRCs) and their affiliates by physicians there knowledgeable in the management of patients with MCI and AD. A few clinical facilities in areas where there are no ADRCs could also be included and in hospitals with expertise comparable to ADRCs. All of the individuals, however, who receive the drug therapy must be in a registry and followed with cognitive testing and monitoring of side effects similar to those in the ENGAGE and EMERGE trial. This will provide a large sample for longitudinal follow-up. The cost of the drug therapy would have to be negotiated with the drug company and would be covered through Medicare, much as some of the cancer drugs in trials that are currently covered, that is, no fees to the patient.
- Do another Phase 3 clinical trial similar to ENGAGE and EMERGE but at high dose and with longer follow-up, although such a blinded trial may not be acceptable because of the possible beneficial results of the EMERGE trial. This would be a factorial design of aducanumab with a non-pharmacological intervention similar to the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial. Individuals would be randomized to the high-dose aducanumab and the non-pharmacological intervention or the non-pharmacological intervention and placebo.[13–15] Participants in the trial should have maximal quality of medical care to control their blood pressure (BP), diabetes, heart failure (HF), and atrial fibrillation. Genotyping should be done especially for apolipoprotein E (*APOE*) ε4 but also for other genes that may determine individuals' benefit. Amyloid imaging or perhaps use of blood biomarkers would be available at entry and in a subsample to measure changes in amyloid in the brain or other biomarkers.

The decision to conduct a third study when there are borderline results with the initial trials may not lead to positive outcomes. The two studies (Expedition 1 and Expedition 2) conducted for 18 months with solaneuzumab in mild–moderate AD patients were considered negative;[16] the primary outcomes were the 11-item Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog-11) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL). However, while the results were negative with the ADAS-Cog-11 in Expedition 2, there was a statistically significant difference between placebo and treated groups when the outcome was measured on the 14-item ADAS-Cognitive (ADAS-Cog-14). In addition, there were statistical differences in the ADAS-Cog 11 and ADCS-ADL in those patients with mild AD. Consequently, it was decided to conduct a third study focusing on mild AD cases, which did not show any differences between placebo and control cases in the primary outcome, the ADAS-Cog-14.[17]

There is a history of similar issues in other important trials.[18–20] The first cholesterol lowering trial, the Clofibrate Trial in 1964, showed that clofibrate was effective in lowering blood cholesterol levels.[10] However, there was an increase in total mortality, which led many to conclude that the cholesterol hypothesis of atherosclerosis and coronary heart disease (CHD) was faulted. In 1985, the cholestyramine trial reported by the NHLBI in the Lipid Research Clinic Program[21] produced equivocal results with regard to reduction in CHD in spite of reduction of low density lipoprotein cholesterol (LDL-C), a positive statistically significant effect noted only in a one-tailed test. There was no effect on total mortality. The drug was approved by the FDA and further studies were done with equivocal results. The drug was used for a limited number of years until the early 1990s when statin trials showed unequivocal benefit of lowering LDL-C on CHD and total mortality, at least initially for those who already had heart attacks, that is, at high risk,[22] and then later years for the general population. The much greater lowering of LDL-C by statins and, more recently, other lipid-lowering drugs, accounted for the greater benefit and reduction in cardiovascular disease (CVD) morbidity and mortality. It took about 25 years of drug trials to substantiate benefit of lowering LDL-C on CHD and total mortality.

Recently, the Systolic Blood Pressure Intervention (SPRINT) trial demonstrated that very substantially lowering BP was associated with a reduction in mortality and in HF but not a significant effect on stroke nor on dementia.[23–25] The magnetic resonance imaging biomarkers also show no effect on brain neurodegeneration. Unfortunately, the trial was stopped very early because of the benefit in reducing HF and mortality possibly precluding a benefit for reducing dementia.

There needs to be a further evaluation of how the AD and dementia trials including how they are done and managed; associated costs; recruitment of participants; maintenance of participants in the study; length of follow-up; management of associated comorbidities, which may be impacting the results of the trial designs that test more than one drug at a time.[15] The reporting of results of trial(s) in peer reviewed publications prior to "public, stakeholder reports" should be a high priority. How long until we have a "statin" for AD?

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CONFLICTS OF INTEREST

Dr. Kuller has nothing to declare. Dr. Lopez served as a consultant for Grifols, Inc.

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