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Editorial

How Will Aducanumab Approval Impact AD Research?

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The accelerated approval of aducanumab (AduhelmTM) by the US FDA is a momentous event. For the first time, a therapeutic agent that targets the neurobiology of Alzheimer's disease (AD) is available for clinical use (1, 2). In addition to the FDA approval of aducanumab, the FDA has also provided "Breakthrough therapy designation" for Lilly's Donanemab and Eisai's Lecnemab which also are monoclonal antibodies that remove brain amyloid plaques and may slow cognitive decline. Aducanumab approval will impact clinical practice. The effects on AD clinical research will be profound in both positive and negative ways. This Editorial reflects the opinion of the leadership of the Alzheimer's Disease Neuroimaging Initiative (ADNI), a large multisite longitudinal observational study with the goal of validating biomarkers for clinical trials. ADNI data have been used to help design and statistically power many AD clinical trials, including the aducanumab studies.

Positive Impacts

Setting aside interpretation of trial data statistical issues, we hope that some patients who receive aducanumab will benefit from aducanumab-induced brain amyloid reduction with slowing of their cognitive and functional decline.

We believe that FDA approval of aducanumab will help change the public perception of AD. Many in the public consider cognitive decline and dementia to be a normal consequence of aging with no effective treatment. This nihilistic view prevents patients and their families from seeking medical evaluation and is one reason why recruitment of participants into AD clinical research, including therapeutic trials, is difficult. Unfortunately, this perception is commonly held by many healthcare providers. The recent approval should help all healthcare professionals to understand that cognitive decline and dementia in older people are caused by diseases, most commonly AD, and that a medical workup for such patients is needed now that an approved treatment which may slow decline is available. We hope that the widespread media attention surrounding the approval will serve to educate the public, promote more patient visits to their healthcare providers, and lead to greater participation in clinical research.

Another potential outcome of aducanumab approval may be more investment by government and the private sector in neurodegenerative disease research. For some time, there has been negative press coverage about failed trials and speculation that amyloid is a failed target. In the past, we have heard from many in the investment community that there is no interest in treatments aimed at amyloid, because they are ineffective. The mood should now shift as the scientific community (admittedly with some exceptions) recognizes that treatments aimed at removing amyloid can be approved. We likewise hope that investment will now extend to all plausible therapeutics aimed at targets such as tau, α-synuclein, and TDP-43, as well as cerebrovascular disease, inflammation, metabolic dysregulation, and other disease mechanisms. The presence of such co-pathologies may contribute to continued cognitive decline after amyloid removal. In the future, more effective treatment for AD may be through combination therapy aimed at multiple pathologies. Therefore, one positive outcome of the aducanumab experience may be increased awareness of the need for more research to develop diagnostics and therapeutics for these co-pathologies.

The approval of aducanumab will likely also increase investment in diagnostics. The use of amyloid PET scans and cerebrospinal fluid amyloid and tau peptide assays will increase because of aducanumab approval.

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There is huge excitement in the AD research community about plasma tests for amyloid, phosphorylated tau, neurofilament light and others; blood tests are certainly less expensive and less invasive than PET scans or lumbar punctures, and more widely available.

Most AD clinical studies, including clinical trials such as the aducanumab trials, draw participant groups that profoundly under-represent people of ethnoculturally diverse backgrounds and people with lower education, and those from low resource backgrounds. It is unclear to what extent insurers will pay for aducanumab and its associated diagnostic costs. Therefore, the approval of aducanumab once again emphasizes the same disparities in healthcare we have seen repeatedly in other disease fields and with COVID-19. All of us involved in this work must strive to be more inclusive and to help reduce dementia disparities.

Negative Impacts

The approval of aducanumab will have some negative effects on AD research. One concern is that this approval might lead to false hope, ultimately causing disappointment and disillusionment. The reported clinical benefits are modest and may not be apparent to individuals. There are also potentially serious side effects, specifically amyloid-related imaging abnormalities (ARIA), which requires MRI monitoring for detection. It is possible that if the treatment is used by inexperienced clinicians, adverse consequences may become more common. Taken together with the costs of treatment and associated diagnostics, this may end up leading to a public sense of disappointment and reduced participation in clinical research.

We believe that in the short term, aducanumab approval is likely to make all types of AD clinical research including observational studies like ADNI, and randomized clinical trials, more difficult. Many AD experts report being swamped with calls from their patients and others asking about aducanumab and requesting visits. As aducanumab becomes available to more and more doctors, especially those involved in research, the resources which are currently devoted to research (clinician time, staff, examination rooms, PET and MRI scanners) will be diverted to provide treatment. COVID-19 has severely slowed clinical AD research and we can expect aducanumab approval to further delay the recovery of research activities. Of course, in time, the growing need for AD specialists, including physicians, neuropsychologists, and nurses, clinical space, and scanners will result in more investment and growth in this area. But research institutions, especially universities where most clinical AD research is performed, are very slow to respond to growing needs. For example, it may take years to find or build space for new MRI or PET scanners in the university environment.

Another way that aducanumab will make clinical studies more difficult is that many patients and their families will choose to be treated with the approved aducanumab instead of joining an observational study such as ADNI or participating in a randomized trial of an unapproved (however promising) treatment. We've seen this story play out in other disease fields - the first approved treatment becomes the preferred treatment for many, and this greatly complicates observational studies and other treatment trials. On the other hand, many studies and trials will adjust their protocols and analysis plans to allow use of aducanumab by participants.

In summary, the FDA approval of aducanumab will have both positive and negative effects. We hope that at least some appropriately treated patients may benefit, and the public and clinicians will become much better educated about AD. Clinical research will be complicated by inclusion of people taking disease-altering therapy. Public resources, notably Medicare, will be strained by the need to provide aducanumab to the large number of appropriate patients. We anticipate a rapid surge in investment in AD treatment centers, diagnostic technologies, as well in developing improved therapeutics which slow, stop, and prevent the progressive symptoms of AD and other neurodegenerative diseases.

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