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Editorial

What does aducanumab treatment of Alzheimer's disease mean for research on vascular cognitive disorders?

Controversial registration of aducanumab for Alzheimer's disease

Despite phenomenal research investments focused on Alzheimer's disease (AD) in the past two decades, it has proven very difficult to develop disease-modifying treatments. The monoclonal antibody aducanumab was approved in June 2021 by the US Food and Drug Administration (FDA) using the accelerated approval pathway despite "residual uncertainties regarding the clinical benefits" [1]. While some researchers considered the decision a major advancement [2], many others did not, seeing the development as a setback in the search for Alzheimer's therapeutics [3,4]. One reason for this is the emphasis in the FDA's decision on a surrogate endpoint, beta-amyloid removal only. To date no anti-amyloid drug, including aducanamab, has demonstrated clinically-meaningful benefit [5].

Post-licensing issues with aducanumab

There are a number of issues that are worth considering when evaluating the approval of aducanamab. First, aducanamab was evaluated in patients with mild cognitive impairment (MCI) or mild stage AD dementia, all of whom were positive for amyloid biomarkers evaluated using amyloid-PET or CSF A-beta40 and A-beta42, and without evidence of territorial stroke, strategic infarcts, or more than 4 microbleeds. Thus, for post-licensing use by clinical teams, expensive and invasive methods may be needed to determine a patient's eligibility [6] prior to administering the drug clinically (though the emergence of plasma biomarkers such as phospho-tau181 may render lumbar puncture unnecessary). Second, for adequate safety management, repeated brain MRI scans are necessary, to detect potential side effects, in particular vasogenic oedema and haemorrhage or micro-haemorrhage during the treatment period [6,7]. Third, due to the high cost per patient not all healthcare systems and patients will be able to afford this treatment. Consequently, only well-resourced specialist units, located predominantly in high-income countries, will likely to be able to deliver this new treatment. Finally, because of the increased risk of haemorrhage, microbleeds or cortical siderosis, off-label use of aducanumab as a treatment for sporadic or hereditary cerebral amyloid angiopathy (CAA) is contraindicated [8]. Hence, in real-world dementia care it is likely that only a minority of patients with AD will achieve access to the treatment.

Following the FDA licensing, aducanumab is the subject of a large observational study that commenced in October 2021, aiming to follow the effects of the drug in 6000 people with clinical AD diagnosis. This study, International Collaboration for Real-World Evidence in Alzheimer's Disease (ICARE-AD) (https://clinicaltrials.gov/ct2/show/record/NCT05097131) is a prospective, single-arm, multi-centre study of aducanumab as prescribed in the post-marketing setting in the US. Clinical investigators will prescribe aducanumab and participants will be treated according to the standard of care. Participants will be followed up for up to 5 years after enrollment and data will be collected at routine visits every 6 to 12 months. The primary outcome measures include a broad spectrum of instruments quantifying, mood, activities of daily, quality of life and other symptom-oriented features. There is also a current clinical trial of aducanumab called EMBARK (https://clinicaltrials.gov/ct2/show/NCT04241068). EMBARK is a single arm uncontrolled trial of aducanumab with enrollment open only to the prior participants of ENGAGE and EMERGE [9]. Essentially, it is an open-label extension of EMERGE and ENGAGE keeping patients on treatment and collecting more data. Both ICARE-AD and EMBARK are sponsored by the license holder of aducanumab.

Implications for research on vascular cognitive disorders

As aducanumab formulations become licensed for treatment of AD, investigators have considered the impact on AD research [10]. An equally valid question that could be put forward is: if aducanumab becomes an established treatment for AD patients, what are the consequences for research on vascular cognitive disorders (VCD)? First, ICARE-AD and other post-licensing studies will collect a wealth of valuable data from well-characterised older patients with AD diagnosis, many of whom will have vascular co-morbidities [11]. Given the high prevalence of cerebrovascular pathology in real-world clinical dementia and MCI populations, both in isolation and concurrently with AD, it is important that the ICARE-AD and other post-licensing studies do not ignore VCD [12]. The possibility that aducanumab may have differential effects in people with AD with or without accompanying vascular disease should also be taken into account. Consequently, it would be sensible to characterize ICARE-AD participants by level of

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accompanying cerebrovascular disease. Until such characterization is undertaken, and safety clearly established in AD patients with accompanying cerebrovascular disease, we suggest that indications for aducanumab treatment should not be widened outside its current FDA labelling.

A second opportunity may arise from the "screening failures" of ICARE-AD. Many patients with suspected AD will undergo initial clinical screening but fail to meet inclusion criteria, hence they will not proceed to aducanumab treatment. The data collected from these excluded patients will nevertheless be valuable. For some patients, detailed phenotyping will be available, including MRI and PET as well as blood, CSF and possibly genotype data. The development of a large cohort of real-world dementia and MCI patients with accurately phenotyped levels of cerebrovascular pathology should be used to learn more about the characteristics and differential diagnosis of VCD. This cohort also offers a potential basis for testing of medical and lifestyle treatment of cerebrovascular disease associated with cognitive impairment. These data will help to inform future clinical trial design and, with appropriate consent for re-contact, may help recruitment for trials with a vascular target or vascular readout.

Third, interest in the field of treatments for dementia is likely to increase. Whatever verdict emerges within the next few years on the use of anti-amyloid treatments in AD, the interested parties – governments, funders and the public – show a hearty appetite for more interventions and more clinical trials in dementia. Vascular treatment targets offer novel approaches, some of which are refreshingly independent of beta-amyloid peptides [13]. These include novel molecules (some in trials for other indications), re-purposing of already-licensed drugs and non-pharmacological interventions [13].

Extensive diagnostic and follow-up procedures, unclear clinical benefit (as it has not yet been demonstrated that lowering of amyloid is related to clinical improvement), high cost per patient, and risk of severe adverse effects [7,14] make it likely that aducanumab will be prescribed only to a limited subset of AD patients. Moreover, the European Medicines Agency (EMA) rejected a marketing authorisation application for aducanumab, December 2021 (https://www.alzheimer-europe.org/news/european-medicines-agency-rejects-marketing-authorisation-application-aducanumab). The decision was based on the ambiguous results on cognition derived from the clinical trials, without primarily focusing on the amyloid lowering effect. Furthermore, it is plausible that aducanamab's licensing by FDA may complicate future research into AD therapeutics by establishing a new "standard of care" on the basis of weak clinical evidence. Regarding VCD, which is the research area that is likely to interest authors and readers of this journal, ICARE-AD and other post-marketing studies may offer opportunities to advance the field. These include rich phenotypic data from the AD patients who are included in those studies and receive aducanumab treatment, many of whom will have comorbid vascular disease. There is also the data taken from the screening failures who do not receive aducanumab, many of whom will have vascular disease. In addition, there is likely to be heightened interest in new dementia treatments, including those with a vascular target. As VCD researchers we are challenged to propose new treatment approaches and novel trials in a post-aducanumab era. We are ready to take up that challenge.

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