Age and Ageing 2021; **50:** 1899–1900
https://doi.org/10.1093/ageing/afab167
Published electronically 14 August 2021

EDITORIAL

Aducanumab and the certainty of evidence

Keywords: aducanumab, Cochrane, dementia, evidence, older people

Key Points

- The decision to approve the monoclonal antibody aducanumab as a treatment for dementia has sparked considerable controversy.
- The trial evidence for clinical efficacy is highly uncertain with conflicting results of trials and small effect sizes.
- The approval was based on aducanumab's ability to reduce amyloid burden; however whether this translates into clinical benefit is also highly uncertain.

The many years, careers and dollars spent in pursuit of a treatment for Alzheimer's disease (AD) dementia finally led on 7 June 2021 to the US Food and Drug Administration's (FDA) approval of Biogen's anti-Aβ monoclonal antibody aducanumab (Aduhelm). Yet this landmark moment has not been a cause of universal celebration. Rather, it has unleashed a storm of controversy in the scientific and lay press, with people on both sides of the argument certain that they are correct.

Proponents of the FDA approval claim that this decision will reinvigorate dementia research and offers hope to the millions of people who are living with the disease. Opponents cite inadequate evidence, as well as cost ($56,000 per year), the vague marketing authorisation (albeit the indications for use have subsequently been mode clearer) and some have voiced concern at the potential role of lobbying from dementia groups who may have received support from Biogen. While these are all important considerations, in Cochrane Dementia we have a primary remit around the first concern—the objective assessment of evidence [1]. So, what is the certainty of the evidence supporting aducanumab?

Assessing the aducanumab evidence is not straightforward. The data on which the FDA reached its decision are not all publicly available, but published accounts of the evidence and its evaluation are consistent [2]. In brief, two randomised controlled trials tested aducanumab at low and high dose in patients with mild cognitive impairment due to AD or mild AD dementia. The primary outcome was change on a global assessment scale [the Clinical Dementia Rating Sum of Boxes (CDR-SB)]. About halfway through recruitment, the sponsor terminated the trials on the basis of a pre-planned futility analysis. However, Biogen subsequently analysed additional data that suggested a statistically significant difference ($P = 0.01$) on the primary outcome in favour of high-dose aducanumab in one of the two trials. In absolute terms the difference from placebo was small (CDR-SB: 0.39 points; where the minimal clinically important difference has been estimated at 1–2 points). Various *post hoc* theories were advanced to explain the difference in results between the two trials. However, these did not persuade the FDA's specialist advisory committee who considered the evidence inadequate and voted against approval (10/11 against, 1 uncertain).

The FDA then decided to re-assess, and subsequently approve, aducanumab under its accelerated approval process. This allows marketing authorisation for a drug that treats a serious condition if benefit is shown on a surrogate endpoint, i.e. 'a marker that is thought to predict clinical benefit but is not itself a measure of clinical benefit'. The authorisation comes with a condition that post-marketing studies will be conducted 'to confirm the anticipated clinical benefit' and Biogen have been given up to 9 years to provide this confirmation. Here, the surrogate marker in question was a reduction in brain amyloid, measured using positron emission tomography (PET).

In this context, the question of certainty of evidence shifts to whether or not there are adequate data to support the claim made by the director of the FDA's neuroscience office that '(Aβ plaque) reduction is reasonably likely to predict clinical benefit'. Aducanumab, like other anti-Aβ monoclonal antibodies, is certainly associated with reductions in the amyloid PET signal. However, for many commentators, the decision to approve the drug on the basis of this non-clinical surrogate is at the heart of the controversy. The approval decision is predicated on a belief in a relatively pure form of the amyloid hypothesis—that amyloid processing, deposition and clearance play a central and necessary role in the pathogenesis of AD dementia. This hypothesis has dominated drug development in AD for many years and continues to have vocal advocates. However, for many researchers, it is a hypothesis that will not die in the face of basic science demonstrating that it is oversimplistic and repeated failures of other amyloid-lowering drugs to show clinical benefit [3].

Two pieces of evidence speak especially persuasively against the expectation that, given enough data and time,

the clinical benefit of amyloid plaque removal would become apparent. In a meta-analysis of data from six trials of anti-Aβ antibodies (solanezumab, gantenerumab and bapineuzumab), all of which effectively clear amyloid plaques, Richard *et al.* [4] demonstrated not only that the evidence was overwhelmingly in favour of no clinical effect, but that a hypothetical trial of 100,000 participants showing a very large difference in favour of the anti-amyloid therapy would be needed just to shift the balance back to clinical equipoise. Secondly, Nicoll *et al.*[5] conducted a neuropathological follow-up of participants in an early trial of active immunisation against Aβ. They found that even those participants who achieved near-complete and persistent removal of amyloid plaques progressed to severe dementia before death.

Evidence should consider both benefits and harms and aducanumab was not without safety concerns in the trials. Cerebral oedema (amyloid-related imaging abnormalities) occurred in over a third of participants receiving high-dose aducanumab of whom nearly 1% had severe symptoms. The remainder needed careful monitoring with imaging and dose adjustments.

In summary, the direct evidence for any clinical benefit from aducanumab is highly uncertain, based on *post hoc* analyses of conflicting trials. However, the certainty of clinical evidence has been rendered irrelevant by the decision to approve aducanumab on the basis of a surrogate endpoint whose status as a 'reasonably likely' predictor of clinical benefit is also highly uncertain. Some commentators are optimistic that this approval offers an opportunity to test the amyloid hypothesis in the real world. Others fear that it will expose patients to a risk of harm for no benefit and at huge financial and opportunity cost. In Cochrane Dementia we hope that the phase 4 studies of aducanumab that are required as part of the approval process will provide the evidence needed to settle the arguments, but this too is by no means certain.

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Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: None.

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Received 2 July 2021; editorial decision 5 July 2021