Controversial Alzheimer's drug should not be approved out of desperation, warn Aussie experts

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Aducanumab, a controversial Alzheimer's disease medication with "questionable efficacy," is under review by the Therapeutic Goods

Administration, but authors of a Perspective published today by the *Medical Journal of Australia* say "science, not desperation" should guide the process.

Aducanumab is a human monoclonal antibody that selectively reacts with amyloid-β, reducing amyloid plaque. The most dominant theory about the development of Alzheimer's disease (AD) is that the initial causative event is a deposition of amyloid-β.

The U.S. Food and Drug Administration (FDA) approved aducanumab for use in AD despite Phase 3 trials being terminated early in 2019 after a futility analysis.

"A subsequent post hoc reanalysis of additional data led to [the FDA] approval on 7 June 2021 via the Accelerated Approval Program, not on the basis of demonstrated clinical efficacy, but on the unproven presumption that reduction of amyloid plaques is 'likely to predict clinical benefit,'" the MJA authors, led by Dr. Andrew Gleason, from the Melbourne Dementia Research Centre at the Florey Institute.

"This approval took place despite the recommendations of 10 of the 11 members of the advisory committee (one abstained). Three FDA advisors subsequently resigned in protest and the FDA commissioner requested an independent inquiry into the process that led to approval of the drug," Gleason and colleagues wrote.

"Proponents of the approval, including the FDA and the Alzheimer's Association, defended the decision by arguing that AD is a serious disease where there is unmet need, and, if there is a chance that a drug could provide a benefit, patients should be allowed access while more data are collected."

So far the evidence does not provide "a compelling case for clinical

benefit," Gleason and colleagues wrote, including two phase 3 trials which found "a small effect size … at 78 weeks … at high but not low dose" in one case, and "no statistically significant benefits" in the other.

The authors also questioned the amyloid-β hypothesis itself, saying "there are no data from clinical trials of aducanumab, or any other source, to indicate that lowering amyloid-β has clear clinically significant benefit."

"Data from other trials to date suggest that amyloid lowering does not have an appreciable effect on cognition, and in some studies, patients treated with amyloid-β-lowering therapies were cognitively worse."

Gleason and colleagues concluded that regulatory approval based on a post hoc analysis was akin to "winning a sharpshooter contest by drawing a bull's-eye around a bullet hole."

"Premature approval without evidence of clinically meaningful benefit from controlled clinical trials is costly to government as well as patients (who are exposed to side effects), may make it harder to recruit to experimental placebo-controlled clinical trials, and could divert research funding away from the development of more effective treatments," they wrote.

"Disease-modifying therapies for AD are urgently needed, but science, not desperation, should guide the approval process."

More information: Andrew Gleason et al, Does the FDA-approved Alzheimer drug aducanumab have a place in the Australian pharmacopoeia?, *Medical Journal of Australia* (2022). DOI: 10.5694/mja2.51408