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EDITORIAL

Aducanumab: evidence from clinical trial data and controversies

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Abstract

Alzheimer's disease (AD) is the most common cause for dementia worldwide. Until recently, all approved treatments for AD were symptomatic and not disease modifying. On 7 June 2021, the US FDA approved aducanumab, a human IgG1 anti-Aβ monoclonal antibody selective for Aβ aggregates, as the first disease-modifying treatment for AD. Aducanumab is approved in the United States for the treatment of mild cognitive impairment or mild-dementia stage of AD. In this Editorial, we review the trial data for aducanumab in the treatment of AD and the controversies that its approval has generated.

Keywords: β-amyloid, aducanumab, Alzheimer's disease, amyloid-related imaging abnormalities, anti-Aβ monoclonal antibody, dementia, neurofibrillary tangles, tau proteins.

Citation

Tampi RR, Forester BP, Agronin M. Aducanumab: evidence from clinical trial data and controversies. *Drugs Context*. 2021;10:2021-7-3. https://doi.org/10.7573/dic.2021-7-3

Introduction

Alzheimer's disease (AD) is a progressive and ultimately fatal neurodegenerative disorder that accounts for 60–80% of cases of dementia worldwide.[1] There is an estimated 6.2 million individuals with AD in the United States alone, with this number expected to nearly double by 2050.[2] AD is the sixth leading cause of death in the United States.[1] Whilst deaths due to stroke, HIV and heart disease decreased between 2000 and 2018, the reported deaths from AD increased by 146.2%. In 2021, the cost of care for individuals with AD and other dementias was estimated to be nearly $355 billion a year and this cost is expected to increase to more than $1.1 trillion a year by 2050.[2]

The neuropathological hallmarks for AD include the following: (1) deposition of β-amyloid (Aβ) peptides, known as amyloid plaques, in the extracellular matrix between neurons, (2) the formation of intracellular neurofibrillary tangles comprised of accumulated hyperphosphorylated tau protein in neurons, (3) neuronal loss, and (4) neuroinflammation.[3] It is postulated that Aβ begins to accumulate in brain tissue approximately one to two decades prior to the onset of clinical symptoms of AD.

The amyloid cascade hypothesis of AD postulates that the accumulation of Aβ results in the dysfunction of neurons that leads, in turn, to the formation of neurofibrillary tangles, the loss of neurons and the depletion of neurotransmitters.[4] The loss of cholinergic neurons in the basal forebrain nuclei in particular results in a general cholinergic deficit that causes short-term memory loss in AD.[5] It is thought that these complex pathologies may occur simultaneously in the brain of individuals with AD.[4]

The known risk factors for AD include older age, a family history of AD, the presence of the apolipoprotein E4 (ApoE) genotype, obesity, hypercholesterolaemia, traumatic brain injury, lower educational levels and depression.[1,2] Diabetes and hypertension, which are risk factors for cerebrovascular pathology, lower the threshold for the clinical appearance of dementia due to development of plaques and tangles. The mutations in the genes *presenilin 1*, *presenilin 2* and *APP* (encoding amyloid precursor protein) are associated with the early-onset, autosomal-dominant variant of AD.

Until recently in the United States, there were only five treatments approved by the US FDA for neurocognitive symptoms of AD.[6] These include three cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and one N-methyl-D-aspartate receptor antagonist (memantine) as well as a combination of donepezil and rivastigmine. The first four drugs are also licensed in the European Union. In the United States, a fixed-dose combination with donepezil and memantine

was approved in 2014 for the treatment of individuals with moderate to severe AD dementia who are stable on donepezil. None of these medications are disease-modifying treatments for AD.

FDA press release

The FDA approved aducanumab for the treatment of AD on 7 June 2021.[7] The drug will be sold as Aduhelm by Biogen, the owner of the drug. The FDA press release explained that Aduhelm was approved using the 'accelerated approval pathway'.[7] This pathway can be used to approve a drug for a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments. Additionally, 'accelerated approval' can be based on the drug's effect on a surrogate end point (in this case, a biomarker) that is reasonably likely to predict a clinical benefit to patients. Furthermore, there is a required post-approval trial to verify that the drug provides the expected clinical benefit. Aduhelm was also granted 'Fast Track' designation, which is provided to expedite the development and review of drugs that are intended to treat serious conditions when the initial evidence shows the potential to address an unmet medical need. The press release also indicated that this is the first new treatment approved for AD since 2003 and is the first disease-modifying therapy. The FDA subsequently updated the prescribing information to clarify that mild cognitive impairment (MCI) and the mild dementia stage of AD were the approved indications for the use of Aduhelm.[8]

Review of data from studies 301 and 302 for aducanumab

All the information included in the next section regarding aducanumab and the two trials conducted by Biogen was obtained from the Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting Briefing Document on 6 November 2020.[9] The disclaimer for the document states that it is available for public release without redaction. We are aware that this particular document was jointly authored by the FDA and Biogen and may have potentially introduced some bias in how the data were interpreted and presented.

Aducanumab is a human IgG1 anti-Aβ monoclonal antibody selective for Aβ aggregates.[9] Biogen conducted two identically designed 18-month-long randomized, double-blind, placebo-controlled, parallel-group studies (301 and 302) that evaluated the efficacy, safety and pharmacokinetic and pharmacodynamic properties of aducanumab. The double-blind placebo-controlled period was followed by a dose-blinded long-term extension. The two studies enrolled a total of 3285 participants at 348 sites in 20 countries. The participants were individuals who were between 50 and 85 years of age, had a diagnosis of early symptomatic AD and were positive for brain amyloid pathology as assessed by PET. Inclusion criteria were (1) participants must have had a baseline Mini-Mental State Examination (MMSE) score of 24–30 and (2) a Clinical Dementia Rating-Sum of Boxes (CDR-SB) global score of 0.5. In the studies, individuals who were ApoE ε4 carriers and ApoE ε4 non-carriers were enrolled. Approximately 80% of participants in both studies had a baseline clinical diagnosis of MCI due to AD and about 20% had a diagnosis of mild AD dementia. Table 1 describes the demographic data for trials 301 and 302.

The primary objective of the studies was to assess the efficacy of aducanumab in reducing cognitive decline measured on the CDR-SB.[9] The secondary objectives were to evaluate the effect of aducanumab on the decline in MMSE, the Alzheimer's Disease-Cognitive Subscale (ADAS-Cog13) and on the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI (ADCS-ADL-MCI). The tertiary efficacy objective for the two studies were to analyse (1) the effect of aducanumab on neuropsychiatric symptoms as measured on the Neuropsychiatric Inventory-10 (NPI-10), (2) the safety and tolerability of aducanumab, and (3) the pharmacokinetic and pharmacodynamic properties of aducanumab.

The biomarkers that were assessed in both studies were as follows: (1) brain amyloid pathology as assessed by

Table 1. Demographic data, intent to treat population.[9]

Study	301 (ENGAGE)	302 (EMERGE)
Total (*n*)	1647	1678
Age in years ± SD	70.1±7.45	70.7±7.43
Female (%)	52.4	51.5
White (%)	75.2	78.4
Education in years ± SD	14.6±3.71	14.5±3.63
ApoE ε4, *n* (%)		
Carriers	69.5	66.8
Non-carriers	30.3	32.8

ApoE, apolipoprotein E; SD, standard deviation.

^{18}F-florbetapir PET, using ^{18}F-flutemetamol in Japan and by measuring cerebrospinal fluid (CSF) Aβ1–42 levels; (2) intracellular tau accumulation as measured by CSF p-tau levels and neurodegeneration as measured by CSF t-tau levels; (3) tau pathophysiology as assessed by ^{18}F-MK-6240 Tau; and (4) brain volume change as measured by MRI.[9] Clinical assessments were conducted at baseline, 6 months, 1 year and 18 months. The amyloid PET was completed at 6 months and 18 months. The CSF and tau PET assessments were collected at 18 months whilst brain MRI scans were done at 6 months and 18 months.

In the two studies, participants were randomized 1:1:1 to low-dose aducanumab, high-dose aducanumab or placebo.[9] The randomization was stratified by ApoE ε4 carrier status. Table 2 describes the dosing strategy for aducanumab in the two studies. An interim analysis was planned after approximately the first 50% of participants in the two studies had the opportunity to complete the week 78 primary efficacy assessment. The interim analysis was prespecified as a futility analysis. There was no possibility of stopping the trial for positive efficacy of the drug. Table 3 provides the efficacy data for trials 301 and 302. Tables 4 and 5 provide biomarker data from the two trials. Table 6 provides the common adverse effects from the two trials.

Aducanumab was associated with dose-related amyloid-related imaging abnormalities related to cerebral oedema (ARIA-E) and to intracerebral haemorrhage (ARIA-H).[9] The risk for these events was greater in ApoE ε4 carriers and tended to occur early (12–32 weeks) during treatment. The risk for intracranial haemorrhage with aducanumab was low and similar to the placebo group. Potentially clinically significant blood chemistry, haematology and urinalysis findings were infrequent and occurred in similar proportions amongst participants in the aducanumab and placebo groups. The investigators did not note any significant changes in vital sign measurements amongst either group, including changes in heart rate and blood pressure, and any changes were similar between the two groups. The occurrence of abnormal electrocardiogram (ECG) findings was also similar between the two groups. One participant in the aducanumab group developed hypersensitivity to the drug and a second participant developed urticaria and angio-oedema during infusions. These reactions resolved in both participants and neither had anti-aducanumab antibodies. The development of treatment-emergent antibodies was <1.0% in all dose groups. Additionally, there was no correlation between the dose of drug and the incidence of anti-aducanumab antibodies. The presence of anti-aducanumab antibodies had no correlation with the development of adverse events. There were no significant differences between the development of suicidal ideation (3.2% *versus* 4.5%) or suicidal behaviors (<0.1% *versus* <0.1%) between the aducanumab 10 mg/kg and placebo groups, respectively.

Finally, the document[9] concluded that the differences in outcomes between Study 301 and Study 302 may have been due to the following: (1) a small number of rapidly progressing

Table 2. Dosing strategy for aducanumab.[9]

Protocols	ApoE ε4 carriers		ApoE ε4 non-carriers	
Versions 1–3	**Low dose**	**High dose**	**Low dose**	**High dose**
	3 mg/kg after titration over 8 weeks	6 mg/kg after titration over 24 weeks	6 mg/kg after titration over 24 weeks	10 mg/kg after titration over 24 weeks
Versions 4–6	3 mg/kg after titration over 8 weeks	10 mg/kg after titration over 24 weeks	6 mg/kg after titration over 24 weeks	10 mg/kg after titration over 24 weeks

Table 3. Efficacy data at week 78, intent to treat population.[9]

Study/scales	301		302	
	Difference amongst individuals treated with aducanumab *versus* placebo			
	Low dose	**High dose**	**Low dose**	**High dose**
CDR-SB	0.18 (–12%), p=0.2250	0.03 (2%), p=0.8330	–0.26 (–15%), p=0.0901	–0.39 (–22%), p=0.0120
MMSE	0.2 (–6%), p=0.4795	–0.1 (3%), p=0.8106	–0.1 (3%), p=0.7578	0.6 (–18%), p=0.0493
ADAS-Cog13	–0.583 (–11%), p=0.2536	–0.588 (–11%), p=0.2578	–0.701 (–14%), p=0.1962	–1.400 (–27%), p=0.0097
ADCS-ADL-MCI	0.7 (–18%), p=0.1225	0.7 (–18%), p=0.1506	0.7 (–16%), p=0.1515	1.7 (–40%), p=0.0006
NPI-10	Not available	Not available	–0.5 (–33%), p=0.3921	–1.3 (–87%), p=0.0215

Negative percentage = less progression in the treatment arm.

Table 4. Change from baseline in biomarkers in Study 302 at week 78.[9]

Biomarkers	Difference amongst individuals treated with aducanumab *versus* placebo, *p* value	
	Low dose	**High dose**
Amyloid PET	−0.179, $p<0.0001$ $n=100$	−0.278, $p<0.0001$ $n=109$
CSF analyte		
β-amyloid1-42 CSF	179.57, $p<0.0001$ $n=33$	318.88, $p<0.0001$ $n=17$
p-Tau CSF	−15.64, $p=0.0035$ $n=33$	−22.44, $p=0.0005$ $n=17$
t-Tau CSF	−86.74, $p=0.0148$ $n=33$	−112.05, $p=0.0008$ $n=17$

β-amyloid1–42, 42-amino acid form of β-amyloid; CSF, cerebrospinal fluid.

Table 5. Change from baseline in Tau PET composite region at week 78.[9]

Biomarker	Difference amongst individuals treated with aducanumab *versus* placebo, *p* value	
	Low dose	**High dose**
Tau PET composite region		
Frontal	−0.049, $p=0.0876$ $n=14$	−0.073, $p=0.0212$ $n=11$
Medial temporal	−0.115, $p=0.0012$ $n=14$	−0.132, $p=0.0005$ $n=11$
Temporal	−0.065, $p=0.1174$ $n=14$	−0.096, $p=0.0304$ $n=17$

All tau PET assessments performed in the placebo-controlled period were pooled from Study 301 and 302 and used as one postbaseline timepoint.

Table 6. Summary of adverse events.[9]

Type	Placebo (%)	Low dose (%)	High dose (%)
Number of subjects with any event	86.9	85.7	91.6
Related drug event	25.1	36.5	51.3
Related serious event	0.7	1.7	2.0
Events leading to study drug discontinuation	4.1	11.1	8.8
Events leading to study withdrawal	2.9	6.7	3.7
Number of deaths	0.5	0	0.8
Amyloid-related imaging abnormalities – oedema (ARIA-E)	2.7	20.5	35.0
Headache	15.2	14.3	20.5
Amyloid-related imaging abnormalities – haemorrhage or superficial siderosis (ARIA-H)	6.5	12.3	19.1
Falls	11.8	12.3	15.0
Superficial siderosis of central nervous system	2.2	5.7	14.6
Diarrhoea	6.8	6.7	8.9

participants in the high-dose group of Study 301 that may have affected clinical outcomes, (2) lower exposures to the target dose of 10 mg/kg in the high-dose group of Study 301 that may have affected clinical and biomarker outcomes, and (3) fewer participants in Study 301 had high exposure to 10 mg/kg dosing and more participants had no exposure to 10 mg/kg when compared to Study 302.[9] There were no imbalances in demographic and disease characteristics that were thought to have contributed to the difference in results. Differences in the incidence, severity, association with symptoms or management of ARIA with potential implications of functional unblinding were not considered factors for the differences in outcomes noted between Study 301 and Study 302.

Statistical review and evaluation of aducanumab by the FDA

The statistical review and evaluation of aducanumab by the FDA stated that the available data did not seem to provide sufficient evidence to support the efficacy of high-dose aducanumab amongst individuals with AD.[10] The reviewers noted several issues with the trial data regarding aducanumab. (1) Both studies were terminated early for futility and were not fully completed, with the data cut-off date being 26 December 2018 and the public futility announcement date being 21 March 2019. (2) There was sporadic unblinding for dose management of ARIA cases, which was noted to be much higher in the drug-treated group. (3) The larger effect that was noted in the ApoE group in the amyloid PET sub-study was in contradiction to what was noted in the clinical outcome data in phase III. (4) In both studies, the correlation between week 78 cerebellum SUVR (standardized uptake value ratio) change and week 78 CDR-SB change was quite small in the high-dose group. (5) The sponsor's assertion about the intermediate dosing early (less than 10 mg/kg doses) in the trial being a challenge was questionable as there was increased placebo progression in the post-amendment protocol version 4 (PV4) and smaller effects were noted on all four key endpoints in ApoE non-carriers, all of whom got the 10 mg/kg dosing from the beginning of the study when compared to ApoE carriers who had to wait until PV4. (6) Data supported by randomization indicating that the low dose in Study 301 was numerically superior to the high dose despite none of the participants having received the 10 mg/kg dose. (7) The distribution of regional enrollment changing over the course of the studies may have confounded the impact of PV4, allowing the $ApoE^{+}$ high dose to reach 10 mg/kg instead of only 6 mg/kg in earlier protocols. The reviewers concluded that there was no convincing evidence from available data that there was a delay in clinical progression of cognitive or functional decline from these studies. They noted that the single positive timepoint was un-replicated and conflicted by the second study. Additionally, the delayed start design with termination for futility did not help with the completeness or interpretability of long-term follow-up data in these studies.

Reviews of evidence by independent sources

The Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee met on 6 November 2020 to discuss the available data from the aducanumab trials. The committee members voted, with 10 members against and 1 member uncertain that it was not reasonable to consider the evidence of clinical benefit from Study 302 as primary evidence of effectiveness of aducanumab for the treatment of AD and the vote being largely based on the conflicting results of Study 302 and Study 301.[11,12]

In their review, Alexander et al. indicate that Study 301 did not meet its primary end point of a reduction relative to placebo in the CDR-SB score.[13] Additionally, no statistically valid conclusions could be reached for any of the secondary end points in this study as per prespecified plans. However, in Study 302, statistical significance was obtained on its primary end point, a treatment effect corresponding to a 22% relative reduction in the CDR-SB outcome for high-dose aducanumab when compared to placebo (p=0.01). However, in this study, the low-dose aducanumab group did not produce statistically significant effects when compared with placebo. Based on the prespecified analytic plan for the study, the ability to assess efficacy with respect to secondary outcomes in both the high-dose and low-dose groups was prohibited. The authors also point out that any post hoc selection of the randomized controlled trial that reached statistical significance without explicitly acknowledging this purposeful choice can introduce a bias. They opined that any post hoc analyses regarding aducanumab provided limited information useful in deciding its benefit and should not be the basis for FDA approval. The authors also noted that the rates of ARIA-E were significantly higher in the high-dose aducanumab group *versus* placebo (35.2% *versus* 2.7%). Additionally, per the FDA's statistical review, 0.9% of participants with ARIA experienced severe symptoms, suggesting evidence for potentially higher risk for those individuals who received high-dose aducanumab. The authors also stated that although the risk of ARIA can be mitigated by close monitoring using imaging techniques and dosing management, they worried as to how consistently and comprehensively this could be achieved in clinical practice. The authors went on to add that although the FDA prefers two positive, adequate and well-controlled trials to demonstrate substantial evidence of efficacy for a new drug, an amendment in 1997 allows the FDA to approve a new drug based on a single study that shows "*substantial evidence of effectiveness*".[14] Morant et al. state in their paper that from 2012 to 2016, any product that was approved based on a single pivotal trial has been associated with statistically significant results ($p \leq 0.005$), and most approvals were supported by additional efficacy data from non-pivotal studies.[15]

Knopman et al. published a critical review of the two aducanumab trials.[16] The authors state that although it is possible that aducanumab has cognitive benefits, the

available data are insufficient to make a "*claim of efficacy*" for the drug. They state that even after considering the issues caused by the termination of these trials prematurely, having only one positive trial with the other trial being negative means that the evidence regarding the drug's efficacy is not conclusive. Additionally, the authors indicate that, although plausible, the claims about lack of sufficient exposure to high-dose aducanumab and the role of variations in placebo group and low-dose group outcomes are also inconclusive. They state that the available biomarker data from both trials do not support a claim of clinically relevant cognitive benefits due to target engagement by aducanumab for Aβ PET and tau PET as neither target engagement was linked to cognition. The authors conclude that there is a need for a third phase III trial that is optimally designed and adequately powered to prove the clinical efficacy of aducanumab for MCI and mild AD.

Liu et al. indicate that, on post-hoc analysis in the EMERGE (302) trial, high-dose aducanumab was shown to be better than placebo on the following scales: −0.39 points on the CDR-SB, 0.6 points on the MMSE, −1.4 points on the ADAS-Cog13 and 1.7 points on the ADCS-ADL-MCI.[17] The ENGAGE (301) trial did not show any benefit for aducanumab on any of the outcomes when compared to placebo: 0.03 points on the CDR-SB, −0.1 points on the MMSE, −0.59 points on the ADAS-Cog13 and 0.7 points on the ADCS-ADL-MCI. The authors question whether the small mean differences on these scales favouring aducanumab in the EMERGE trial and the negligible effect in the ENGAGE trial should raise queries as to whether these statistically significant outcomes provide any clinically meaningful effects for the drug. Additionally, they state that the application of the FDA's own guidance, namely that "*one positive well-controlled trial that is supported by confirmatory evidence* [is] *substantial evidence of effectiveness without considering mean difference or effect size*"[18], to the above-mentioned trials has created considerable controversy.

The Institute for Clinical and Economic Review report from May 2021 concluded that there was uncertainty about the benefits of aducanumab when used amongst individuals with AD and that there was evidence for harms with its use, with the current evidence being insufficient to determine the net health benefit of aducanumab.[19] Additionally, the report stated that when base-case results were calculated from both the healthcare system and the modified societal perspectives, the cost-effectiveness threshold prices for aducanumab ranged from an annual price of $2560 to $8290. The annual cost of $50,000 for aducanumab that has been suggested by market analysts would not be commensurate with its clinical benefits.

A recent report by an expert panel recommended the use of aducanumab for individuals with MCI and mild dementia due to AD.[20] The panel also recommended titrating aducanumab to the highest dose (10 mg/kg) to maximize the opportunity for efficacy. They recommended dose interruption or treatment discontinuation for symptomatic ARIA and moderate-to-severe ARIA. The panel recommended MRIs of the brain prior to initiating therapy, during the titration of the drug and at any time that the patient has symptoms suggestive of ARIA and emphasized the importance of clearly discussing the following with the patient and their care partners: (1) indications for treatment, (2) expected outcomes of treatment, (3) potential risks and adverse effects of treatment, (4) required safety monitoring during treatment, and (5) uncertainties that remain regarding this treatment due to individual responses and benefits.

Although many experts have reviewed the data from the aducanumab trials and published their commentaries based on this, the trial data have not been published in any peer-reviewed journal.

Controversy

The FDA approval of aducanumab has generated significant controversy.[21,22] Alexander and Karlawish report the following issues with the approval of aducanumab. Firstly, the committee that reviewed the drug was not informed that the accelerated approval pathway was being considered for approval. Secondly, a post-approval confirmatory trial will not be completed until 2030. Thirdly, it remains unclear whether Aβ is a valid surrogate for the treatment of AD and whether it can be used in routine clinical practice and there is an unclear relationship between Aβ reduction and cognitive improvements. Further, there has been a negative effect on drug development and regulation, with pharmaceutical companies seeking approval for drugs that reduce Aβ or other biomarkers but with unclear clinical benefits. Additionally, patients with AD are dropping out of important clinical trials to take aducanumab, and there have been multiple issues with drug labeling, including indications and the dosing of the drug. The monitoring for ARIA via brain MRI scanning would add to the cost and complexity of care of individuals with AD. Importantly, there is a high annual cost for the drug per patient (at $56,000) when the health gains from the drug is valued at $2500–$8300 per year and there is an out-of-pocket copay of up to 20% of the total yearly cost for the drug. Finally, the approval has led to difficult discussions for clinicians with patients and families regarding the efficacy of the drug, indications, possible need for genetic testing, monitoring for side-effects and cost of the drug, including copays.[23] Despite the concerns raised by the approval of aducanumab, the FDA recently granted breakthrough status to two prospective AD treatments: Eli Lilly & Co.'s donanemab and Biogen and Eisai's lecanemab.[24]

The FDA granting of the approval for aducanumab has sparked investigations both in the US House and at the Department of Health and Human Services.[25] Two large healthcare systems in the United States (Cleveland Clinic and New York's Mount Sinai Health System) have stated that they have decided not to carry aducanumab in their formulary.[26]

Evolving treatments for AD

In a critical appraisal of monoclonal antibody therapies that target Aβ plaque formation and removal in AD, Decourt et al. indicate that lecanemab, solanezumab, crenezumab, donanemab, and ganterenumab are being studied in individuals with AD.[27] Although these drugs are relatively safe for use in humans, they have had limited positive outcomes in the clinical trials. Additional drug trials for AD that are currently under way include those of (1) a tau aggregation inhibitor (LMTX); (2) inflammation-targeting drugs (ALZT-OP1, a nasally inhaled cromolyn, a mast cell stabilizer + oral ibuprofen, a non-steroidal anti-inflammatory agent; COR388, which irreversibly inhibits gingipains; and masitinib, a selective tyrosine kinase inhibitor); (3) AGB101 (levetiracetam repurposed as a synaptic vesicle glycoprotein 2A (SV2A) modulator); (4) blarcamesine (ANAVEX2-73, a sigma-1 receptor agonist); (5) CAD106 (second-generation active Aβ vaccine); (6) icosapent ethyl; (7) the Plasma Exchange – Alzheimer's Management by Albumin Replacement (AMBAR) trial; and (8) troriluzole (BHV-4157, a prodrug conjugate of riluzole).[28] Results from these trials are currently awaited.

Future directions

A RAND corporation analysis found that if a paradigm shift happens in preventing disease progression in people with preclinical or prodromal AD to clinical AD, the healthcare system in the United States would be ill-prepared to handle the expected cases of individuals with AD who will be awaiting treatment.[29] It is projected that individuals would have to wait an average of 18.6 months for treatment between 2020 and 2040, when it is expected that approximately 2.1 million individuals will develop AD whilst on waiting lists for treatment. The provision of care would be constrained by the limited capacity of dementia specialists to evaluate and diagnose patients and by limited access to imaging sites to confirm the diagnosis of AD and infusion centres to deliver the treatment. Additional challenges in providing care would be issues regarding payments for treatments, regulatory changes, workforce expansion, and planning and coordination of care both at the national and local levels along with awareness campaigns. The analysis also states that no individual stakeholder will be able to coordinate the care needs of all individuals with AD. The report recommends starting timely collaborations between the stakeholders to address all obstacles in providing care to individuals with AD. Stakeholders include individuals with AD, their families and caregivers, clinicians, healthcare systems, health insurance companies, the pharmaceutical industry and various governmental agencies, amongst others. Additionally, we foresee issues of equity in access to treatment of AD based on lack of knowledge, stigma and cost of treatment, especially amongst minorities and ethnic communities.

Conclusions

Irrespective of the controversy surrounding the approval of aducanumab, it is clear that all the stakeholders involved in the care of individuals with AD must act in cohesion to develop clinical guidelines and protocols for the appropriate use of this newly approved medication. Inclusivity and equity should be paramount when developing these guidelines and protocols. Despite the subsequent restriction by the FDA of aducanumab for those individuals with MCI and mild AD, many critical questions remain. The FDA label does not specify the requirement for a positive amyloid biomarker (amyloid PET, CSF or serum biomarkers) prior to treatment. Clinical guidelines will need to address both safety monitoring and clinical efficacy outcomes. For example, how long should an individual with MCI, a CDR of 0.5 and an MMSE at baseline of 25 be treated with aducanumab? Should there be cut-offs for treatment beyond a specified time period (e.g. 18 months) based on reduction of brain amyloid or a continued decline in cognition and functioning past a certain CDR or MMSE score? How will healthcare systems address equity in terms of timely clinical assessment and affordability of aducanumab? Finally, will insurers come together to establish clinical safety and outcome standards that were not included in the FDA's label for aducanumab?

Regardless of the availability and eventual post-marketing outcomes of aducanumab, clinicians and researchers alike must strive to further develop and implement integrated care models for individuals with MCI and AD dementia to improve quality of life and ease the suffering and consequences of caregiving. However, the controversies surrounding the FDA approval of aducanumab are worthy of further investigation so that the public regains trust in the review process not only for the potential promise of aducanumab but, even more importantly, for the future development of desperately needed disease-modifying therapies for this epidemic of our times.

Contributions: RRT completed the literature search, reviewed the data and wrote the initial draft of the manuscript. BF and MA reviewed the draft of the manuscript and made suggestions/additions/corrections to it. RRT completed the final revisions on the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: RRT has none. BF reports grants and other from Biogen during the conduct of the study and grants from Lilly, Eisai, NIH, Rogers Family Foundation and Spier Family Foundation and other from Acadia Pharmaceuticals, outside the submitted work. MA reports consulting for Biogen, Otsuka and Eli Lilly. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2021/09/dic.2021-7-3-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/aducanumab-evidence-from-clinical-trial-data-and-controversies

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Provenance: Invited; externally peer reviewed.

Submitted: 13 July 2021; **Accepted:** 6 September 2021; **Publication date:** 4 October 2021.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

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