General

Aduhelm, a novel anti-amyloid monoclonal antibody, for the treatment of Alzheimer's Disease: A comprehensive review

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Alzheimer's disease (AD) is the most common form of dementia affecting millions of individuals, including family members who often take on the role of caregivers. This debilitating disease reportedly consumes 8% of the total United States healthcare expenditure, with medical and nursing outlays accounting for an estimated $290 billion. Cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists have historically been the most widely used pharmacologic therapies for patients with AD; however, these drugs are not curative. The present investigation describes the epidemiology, pathophysiology, risk factors, presentation, and current treatment of AD followed by the role of the novel monoclonal antibody, Adulhelm, in the treatment of AD. Currently, Adulhelm is the only Food and Drug Administration (FDA) approved drug that acts to slow the progression of this disease. Adulhelm is an anti-amyloid drug that functions by selectively binding amyloid aggregates in both the oligomeric and fibrillar states. Studies show Adulhelm may help to restore neurological function in patients with AD by reducing beta-amyloid plaques and reestablishing neuronal calcium permeability. At present, there is concern the magnitude of this drug's benefit may only be statistically significant, although not clinically significant. Despite skepticism, Adulhelm has proven to significantly decrease amyloid in all cortical brain regions examined. With such high stakes and potential, further research into Adulhelm's clinical efficacy is warranted in the treatment of AD.

INTRODUCTION

Alzheimer's disease (AD) is defined as a progressive degenerative brain disease that insidiously takes over the memories, cognitive function, and livelihood of those diagnosed. AD was first described as a serious cortical disease by Alois Alzheimer after finding massive neuronal loss and amyloid plaques in the brain of a patient who suffered from alterations in personality and loss of memory.[1]

Microscopic changes in the brain occur long before the first onset of symptoms and thus long before the diagnosis. The severity of symptoms is classified based on the level of interference with one's ability to perform everyday tasks. Diagnosis of AD lies on a spectrum ranging from preclinical AD with little to no symptoms and extending to severe debilitating AD.[2] Early stages of symptomatic AD first affect cognitive function. What begins as subtle difficulty learning and recalling new information, insidiously progresses to episodes of disorientation and confusion. Later stages manifest with more severe symptoms such as changes in behavior and mood along with physical symptoms such as difficulty swallowing and speaking.[2] The duration of each stage and rate of progression varies and is influenced by factors such as genetics, age, and predisposing conditions.[3]

As the disease progresses, patients are slowly stripped of their independence resulting in an inevitable reliance on caregivers. An estimated 83% of caregivers to older adults in the united states (US) are unpaid family members, friends, or others.[2] The level of responsibility placed on the caregivers of AD patients often requires additional help from

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health care and support from social institutions.[4] AD has been reported to consume 8% of the total US healthcare expenditure, with medical and nursing outlays accounting for an estimated $290 billion.[5] AD patients account for twice the amount of hospital stays as compared to other elderly citizens and increased stays in skilled nursing facilities and home healthcare visits.[2] Development of a curative treatment stands to not only impact patients and their families, but also the healthcare system and overall economy.

METHODS

The present investigation is a narrative review. In 2021, a comprehensive search was performed using the PubMed database for studies related to the topic of aducanumab for AD. We searched the following keywords: AD, aducanumab, Aduhelm, dementia, clinical trials, *Emerge, Engage*. Priority for inclusion was given to recent manuscripts (within the last three years), but relevant papers older than three years were also included. An attempt to search for, use, and cite primary manuscripts whenever possible was also made. This article, therefore, is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

AD is the most common form of dementia. According to the World Health Organization (WHO), around 50 million people worldwide have dementia of which AD is thought to contribute to 60-80% of cases. While some cases are pure AD, the greater majority are mixed dementias further complicating early recognition and diagnosis.[6] Of mixed dementia, vascular dementia and Lewy body dementia are the most common.[6]

According to the Alzheimer's Association, 1 in 9 Americans aged 65 or older has AD. An estimated 6.2 million Americans 65 years or older have AD in the year 2021.[2] At age 45, the estimated lifetime risk for AD was found to be 1 in 5 (20%) for women and 1 in 10 (10%) for men; the risk further increases after the age of 45.[3] Women appear to be diagnosed with AD more than men; almost two-thirds of Americans diagnosed with AD are women.[7] This observed difference has varied throughout different studies and regions and is therefore suggested to be due to women's average longer lifespan. As for racial and ethnic differences, underrepresented groups appear to demonstrate a higher prevalence of AD in comparison to the white population.[7] A study reported that 18.6% of African Americans and 14% of Hispanics age 65 and older have AD compared with 10% of Caucasian seniors.[7] However, studies assessing health and socioeconomic factors suggest racial and ethnic differences in dementia risk do not persist.[3] This suggests healthcare disparities and socioeconomic factors play a stronger role than that ethnicity and race.

According to the Centers Disease Control and Protection (CDC) data, the overall geriatric population is projected to grow from 420 million to 1 billion from the year 2000 to 2030.[8] As for AD, by the year 2050, a projected 12.7 million Americans aged 65 and older are expected to be diagnosed.[2] With a growing elderly population and projected AD growth, focusing on better management of risk factors and potential treatment is of the utmost importance.

RISK FACTORS

AGE

Age has been demonstrated in multiple studies to be a strong risk factor for the development of AD.[9,10] One study reported a 19% increase in prevalence in individuals aged 75-84 years. This further increases to 30-35% in those of 85 years and greater.[10] Related to similarities in pathology, AD was once thought of as an accelerated form of aging.

GENETICS

Genetic predisposition to AD has been studied for years and plays a role in the pathogenesis of both early and late-onset AD. Early-onset AD includes individuals under the age of 65 and is associated with mutations in amyloid precursor protein (APP), presenilin (PSEN) 1, and PSEN2 genes. PSEN1 has been correlated with 80% of early-onset AD compared to 5% associated with PSEN2.[11] In contrast, polymorphisms of the apolipoprotein-E (APOE) gene have proven to be of importance in the development of sporadic late-onset AD.[12] While the ε3 allele is the most common variant, the ε4 allele of the APOE gene has shown to be the strongest genetic risk for the development of sporadic AD. Conversely, the ε2 allele has demonstrated a protective role in the development of disease.[13]

ACQUIRED RISK FACTORS

Various acquired risk factors have also been proven to influence the development of AD. An early-life risk factor includes the level of education achieved.[14] Mid to later-life risk factors includes hypertension, hyperlipidemia, diabetes, obesity, cerebrovascular disease, alcohol abuse, smoking, traumatic brain injury (TBI), depression, and social isolation.[14,15] Notably, cerebrovascular disease and dementia share many common risk factors such as smoking and diabetes.[3] Studies have found a twofold increase in the risk of dementia following a stroke independent of cognitive changes prior to the incident.[11] A reduction in blood supply to the cerebrum and disruption in the blood-brain barrier may predispose to amyloidogenic processes. Similarly, hypertension increases the risk of AD development due to vascular wall changes and disruption of the blood-brain barrier.[11]

EPIGENETIC CHANGES

Many researchers hypothesize that pathologic epigenetic changes play a role in the development of AD. A "two-hit" hypothesis proposes the primary disruption within the associated regulatory genetic sequences is led by environmental stress.[16] The second hit is a result of further stress potentially perpetuated by poor diet, head trauma, or altered gene expression.[16,17] In AD patients with a history of TBI, increased APP, and dystrophic neurites have been observed.[10] Similarly, chronic traumatic encephalopathy

(CTE) is a neurodegenerative tauopathy thought to be secondary to repetitive head trauma.[17]

PATHOPHYSIOLOGY

The neuropathology of AD is composed of positive lesions, related to an accumulation of abnormal protein deposits, and negative lesions, due to neuronal loss and atrophy.[18–20] One of the most accepted theories regarding AD is the amyloid cascade, which refers to an imbalance between the production and clearance of proteins.[11] Under normal conditions, APP is cleaved by α-secretase and y-secretase. When cleaved by β-secretase and ν-secretase, beta-amyloid (Aβ) fragments are produced and induce amyloidogenic processes.[21] Extracellular accumulations of Aβ40 and Aβ42 due to abnormal precursor processing leads to the formation of senile plaque lesions. The Aβ42 peptide has demonstrated an increased likelihood of aggregation as compared to Aβ40, and immunohistochemistry has revealed higher concentrations of Aβ42 in amyloid plaques of AD patients.[11] In addition, phosphorylated tau proteins form neurofibrillary tangles intraneuronally.[6,11] Accumulation of these abnormal proteins not only leads to plaque formation but also activation of microglia and reactive gliosis of astrocytes. This ultimately leads to toxic effects on neurons causing atrophy, neurotransmitter loss (such as acetylcholine), and eventual loss of cognitive function.[6,11,18–20]

PRESENTATION

AD presents insidiously and with a spectrum of symptoms including progressive loss of memory, confusion, and disorientation. Cases may present differently and often in a subtle progressive fashion that goes unnoticed for extended periods of time. Symptoms are frequently first noticed by family members and reported several years prior to a confirmatory diagnosis.[21] The time until the diagnosis can be further complicated by misdiagnosis.

An amnestic presentation is most common with the impaired recall of recently learned information. However, non-amnestic findings can also be seen such as language deficits manifesting as trouble word-finding.[3,22] In addition, impaired facial recognition, spatial cognition, and object agnosia can also be seen in later diseases.[22] This is often reported as getting lost in familiar places or failure to recognize objects or individuals that are familiar to them. While these deficits may present in a subtle manner or be attributed to old age, deficits in executive functioning such as impaired reasoning, judgment, and problem-solving are often most prominent to surrounding friends and family.[22]

Imaging abnormalities may be included in the presentation and diagnosis of AD. Gross anatomic changes seen in AD include widening of sulcal spaces, narrowing of gyri, and enlargement of lateral ventricles secondary to atrophy.[6] Amyloidosis of the brain may be seen in neocortical areas spreading to subcortical structures.[11] However, AD can only be diagnosed with complete certainty via microscopic examination after death.

Throughout the course of the disease, concomitant neuropsychiatric disturbances are often reported and elicit immense stress on caregivers. Symptoms may mimic frontotemporal dementia including apathy, impulsivity, and agitation.[17,23] In more advanced stages, delusions and hallucinations can be seen. Visual hallucinations have been attributed to the loss of cholinergic innervation.[24] Depressive symptoms are also very common in AD and are reported in about 20-30% of patients.[25,26] There has long been a suggested relationship between the two, however, it remains unclear whether depression is a risk factor or an early manifestation of the disease. Ultimately, AD presents with various symptoms in an unpredictable fashion. With improved detection and treatment there is the hope of preventing early progression and cognitive decline.

CURRENT TREATMENT OF ALZHEIMER'S

Cholinesterase inhibitors and memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, have historically been the most widely used pharmacologic therapy for patients with AD. However, these drugs are not curative. The cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine are typically administered at the diagnosis of mild AD. Memantine is normally reserved for adjunctive therapy in patients with moderate disease and an associated decreased ability to complete activities of daily living. While these drugs have been shown to enhance the quality of life by providing symptomatic therapy, they do not change the disease progression, rate of decline, or overall pathological burden.[27] Treatment regimens may be combined with non-pharmacologic options such as aromatherapy, pet therapy, music therapy, and individual recreational activities. The exact efficacy of these non-pharmacologic treatment strategies is uncertain as most studies are limited by poor design, inadequate sample size, and a lack of blinding.[28] The most successful evidence-based approaches are individualized for each patient's unique needs and response to treatment. Some patients with mild AD may respond best to physical, emotional, and social stimulation, while other patients may need more involved cognitive behavioral therapy and pharmacologic therapy.[27,28]

A 12-Month, randomized, open-label trial conducted by Cumbo et al[29] investigated the differential effects of AD medications on behavioral and psychological symptoms of AD. The study suggests that memantine and rivastigmine have the most profound effects on these symptoms with minimal side effects in mild to moderate AD patients.[29] These properties have important implications on a patient's course of care as behavioral symptoms are often the most burdensome for the healthcare team or caretaker.[27] Additionally, attenuating behavioral symptoms may prevent institutionalization and the need for pharmacotherapy with other supplemental drugs (e.g. selective serotonin reuptake inhibitors, atypical antipsychotics). However, the literature review of the cost-effectiveness of the drugs does remain inconclusive.[30]

In search of greater efficacy in pharmaceutical management, numerous clinical studies involving the combination of disease-modifying agents with cholinesterase inhibitors or memantine have been introduced. The goal of combination therapy for AD is to target alternative pathophysiologic pathways that are not influenced by the standard

of care alone. In addition to a more sophisticated counter to the disease process, benefits of combination therapy include the ability to utilize smaller therapeutic doses of the equivalent monotherapy drug which may reduce costs and side effects of treatment.[31] One approach, taken by several of these disease-modifying therapies, is to target the amyloid cascade. Some of these drugs have been tested in phase III trials; however, they have failed to meet the primary endpoint. Postulations as to why these drugs have failed include delayed pharmaceutical introduction after which amyloid-lead destruction becomes too extensive. Future studies can explore introducing anti-amyloid therapies earlier in the AD course, possibly before symptoms ever develop.[31] Another potential pathway to be intercepted involves tau-targeted therapy. Strategies for preventing hyperphosphorylation using both lithium and valproic acid have been introduced, but random control trials of these agents proved unsuccessful.[32] Although these disease-modifying agents have yet to provide proof of significant deceleration of AD, they have augmented our current knowledge of the disease and have shown that improved treatment is a feasible goal. Until then, combination therapy with cholinesterase inhibitors and memantine remains the most efficacious option.[33]

ADUCANUMAB DRUG INFORMATION

Developers of the anti-amyloid drug aducanumab (marketed as Aduhelm) have reported positive findings in phase III trials.[34] The medication functions as a monoclonal antibody targeting Aβ fibrils and soluble oligomers that contribute to AD development. In an early phase, 165 patients with prodromal or mild AD received variable intravenous (IV) doses of the agent. Remarkably, amyloid plaques were considerably decreased in all cortical brain regions examined. However, clinical effects were mostly insignificant.[34,35] Still, these results undeniably showed aducanumab's potential as an amyloid destroyer in future therapies and inspired a myriad of research involving the drug.

Engage and *Emerge* are perhaps the most well-known phase III trials of aducanumab. Using the Clinical Dementia Rating Scale sum of boxes (CDR-SB) in individuals with mild cognitive impairment (MCI) and mild dementia due to AD, the *Emerge* trial showed a 22% decreased rate of cognitive decline in the group of participants receiving high-dose aducanumab compared to that of the placebo group after 78 weeks of study. The experimental group in the *Engage* trial, however, declined more rapidly than the placebo. Positron Emission Tomography (PET) imaging in both groups showed a dose-dependent decrease in amyloid deposition.[36] After these trials, a biologics license for aducanumab was submitted to the Food and Drug Administration (FDA). The drug was approved in 2021. Of note, the drug has a broad label and is approved for patients across the full spectrum of disease severity despite the clinical trials only including subjects with mild disease.[34–36]

ADUCANUMAB MECHANISM OF ACTION

The logic behind anti-amyloid drug therapy can be simplified by the following: the removal of plaques disrupts the major pathogenic process vital to the progression of AD thus slowing the development of the disease. Currently, aducanumab is the only FDA-approved drug that achieves this purpose. The drug functions by selectively binding amyloid aggregates in both the oligomeric and fibrillar states rather than amyloid monomers.[37] This binding discrimination by the drug is what distinguishes aducanumab from its contemporary Aβ immunotherapeutic agents. The Aβ aggregates have been shown to exert neurotoxic effects while monomeric Aβ has exhibited beneficial neurological functions.[37,38] Although other monoclonal antibodies have overlapping binding sites on amyloid, aducanumab provides unique amino acid interactions which allow for more shallow and compact binding with minimized interactions by the epitope scarce monomers. Conversely, the high affinity for aggregates can be explained by a greater concentration of epitopes specific for the monoclonal antibody granting a greater affinity.[38] Researchers have further investigated the binding mechanisms of aducanumab using molecular dynamics simulation technology in of hopes to further optimizing selectivity, which may lead to smaller therapeutic doses and greater efficacy.[39]

ADUCANUMAB PHARMACOKINETICS/ PHARMACODYNAMICS

Aducanumab dramatically reduces the generation of Aβ oligomers through interrupting amyloid aggregation kinetics, a multistep process that includes primary nucleation from monomeric protein and secondary nucleation on existing fibrils. Pharmacodynamic studies of aducanumab have shown that the drug binds fibrils and targets them for microglial-mediated removal, interrupting the bridge between neuroprotective amyloid monomers and neurotoxic amyloid oligomers.[40] Before aducanumab can achieve these effects however, therapeutic levels must be able to cross the blood-brain barrier and persistently promote amyloid aggregate destruction. The drug reaches maximal clinical benefit around 5 months of use due to a long half-life. Several other variables may influence the lag period including the amount of time needed to remove amyloid plaques, individual amyloid burden, APOE ε4 genotype, age, and disease severity.[39–41] This may explain why the high-dose group in the *Emerge* trial resulted in the most significant decrease in the rate of cognitive decline; this group could have had relatively more patients achieve a sustained steady-state in the brain.[41]

CLINICAL STUDIES ON ADUCANUMAB

PRE-CLINICAL STUDY FOR EFFICACY OF ADUCANUMAB IN MICE

A placebo-controlled experiment in mice was carried out to observe aducanumab's efficacy in Aβ plaque degradation.[42] Mice were genetically modified to overexpress APP

to enhance cerebral Aβ plaque formation. A chimeric analog to aducanumab appropriate for mice was used to reduce the size and number of these plaques. Non-placebo mice were administered the aducanumab analog either acutely or chronically. In 22-month-old mice receiving acute immunotherapy, craniotomy was performed and the aducanumab analog was applied directly to the mouse's brain. In those receiving chronic immunotherapy, mice were injected with the aducanumab analog once per week for 6 months beginning at 18 months of age. The mice's brains were imaged at the beginning and end of the experiment using fluorescent microscopy to tag Aβ plaques. Immunohistochemistry was also employed before and after treatment to observe the regulation of the following: inositol trisphosphate (IP3) receptor, NMDA receptor, ryanodine receptor (RYR), and visinin-like-protein (VILIP)-1.[42]

Treatment with the aducanumab analog showed mixed results on its ability to reduce the number of Aβ plaques in mice. Mice that received acute treatment with aducanumab analog experienced a greater decrease in Aβ plaques than mice who received placebo. Acute topical treatment with the analog was associated with a ~48% reduction in the number of Aβ plaques, while control mice showed a ~14% reduction in Aβ plaques ($P < 0.0001$). However, chronic treatment with aducanumab analog did not show a significant reduction in the number of Aβ plaques relative to the control mice ($P = 0.35$). Also, despite its ability to degrade existing plaques, acute treatment with aducanumab analog did not show any significant effect on reducing the formation of new Aβ plaques relative to control ($P = 0.98$). These findings suggest that aducanumab may be efficacious at reducing preformed Aβ plaques in patients but may not significantly prevent new Aβ plaque formation.[42]

This study's findings also indicate that aducanumab may benefit patients with AD through the replenishment of cerebral intracellular calcium levels.[42,43] Disruption in the regulation of intracellular calcium is implicated in several neurodegenerative conditions such as Parkinson's, Huntington's, and AD. NMDA receptors are necessary for the homeostatic maintenance of intracellular calcium in neurons, and Aβ plaques have been shown to increase the clearance of NMDA receptors from neuronal cell surfaces.[43] In mice that received chronic treatment, the aducanumab analog was found to prevent calcium overload ($P < 0.05$) and increase NMDA receptors' permeability to calcium relative to controls ($P < .05$). The aducanumab analog used was also found to restore sarcoendoplasmic reticulum calcium ATPase (SERCA) pump regulation which remained disrupted in control mice ($P < 0.001$). These results show aducanumab may help to restore neurological function in patients with AD by reducing Aβ plaques and reestablishing neuronal calcium permeability.[42,43]

PHASE I CLINICAL TRIALS

Aducanumab's first dose-escalation trial in humans was a randomized, double-blind, placebo-controlled, single-dose-escalation phase I clinical trial.[44] The study included 53 participants, 39 received aducanumab and 14 received a placebo. The aducanumab group received increasing doses (0.3, 1, 3, 10, 20, 30, or 60 mg/kg) of aducanumab over the course of the trial. Only 3 participants received the maximum 60mg/kg dose. In this study, the pharmacokinetics and side effects of aducanumab were determined.[44]

Aducanumab was found to be well-tolerated up to a dosage of 30 mg/kg. In patients who received ⩽ 30 mg/kg, the 3 most reported symptoms were headache, diarrhea, and upper respiratory tract infection. Alzheimer's related imaging abnormality-edema/effusion (ARIA-E) was the most severe side effect and was present in the 3 patients who received the 60 mg/kg dose. Though each case of ARIA-E had transient-related complications, all were resolved. The pharmacokinetics of aducanumab, as determined by this study, showed increasing doses did not significantly alter drug half-life, rate of clearance, or volume of distribution. Aducanumab's pharmacokinetics were found to behave in a linear, dose-dependent manner. The pharmacokinetic profile and observed side effects were found to be safe enough to support future trials.[44]

In 2012, aducanumab entered a randomized double-blind, placebo-controlled phase Ib clinical trial, entitled *Prime*.[35] In this trial, 165 individuals with mild AD or MCI were administered 1, 3, 6, or 10 mg/kg of aducanumab once per month for 12 months. This study measured aducanumab's ability to reduce the size and number of Aβ plaques as well as its effects on cognitive function. These effects were evaluated using PET standard uptake volume ratio (SUVR), mini-mental state examination (MMSE), and CDR-SB. Aβ PET images were taken before starting treatment, then at 26 and 54 weeks after the first treatment. There were 125 individuals who completed the trial.[35]

Aducanumab demonstrated significant benefit in the reduction of Aβ plaques in patients with mild AD or MCI in this trial.[35] SUVR scores were lower relative to baseline in participants who received the 10, 6, and 3 mg/kg monthly doses of aducanumab ($P < 0.001$). This reduction in Aβ plaque accumulation was observed in patients receiving treatment regardless of whether they had MCI or mild AD and whether they were APOE ε4 carriers. Aβ plaque degradation was visible throughout the brain excluding the 2 regions where Aβ plaque formation was not anticipated: the subcortical white matter and the pons.[35]

Results from the *Prime* trial indicate that aducanumab may mitigate cognitive decline in patients with mild AD or MCI.[35,45] Participants with PET SUVR scores that decreased by >1 standard deviation below those of placebo participants observed benefit in the preservation of functioning mental status. These cognitive benefits were not appreciable until treatment was carried out for 12 months despite earlier detectable decreases in Aβ plaques.[35] Aducanumab was found to decrease the rate of progression of cognitive symptoms of AD on the MMSE after one year of monthly treatment at doses of 3 and 10 mg/kg ($P < 0.05$).[35,45] However, patients treated with aducanumab were also observed to have an increasing dose-dependent risk of developing ARIA-E relative to patients receiving a placebo. Forty-one percent of participants receiving 10 mg/kg aducanumab developed ARIA-E while only 6% receiving 3 mg/kg aducanumab developed ARIA-E.[35] This study found that aducanumab provides benefits in managing the mental status of patients with Aβ plaque formation, but also increases their risk of developing ARIA-E.[35,45]

PHASE III CLINICAL TRIALS

Two identical phases III double-blind, randomized, placebo-controlled trials for the use of aducanumab to treat AD were begun in September 2015.[46] These trials were entitled *Emerge* and *Engage*. Each patient, diagnosed with MCI or mild AD, was administered either low-dose or high-dose aducanumab once every 4 weeks for 18 months. Dosages were appropriated according to whether patients carried the APOE ε4 allele. The low dose was 3 mg/kg for carriers of the APOE ε4 allele and 6 mg/kg for those who were non-carriers. The high dose was 6 mg/kg for carriers and 10 mg/kg for non-carriers. Ultimately, 1,643 patients completed the *Emerge* trial and 1,647 completed the *Engage* trial. The primary objective of these trials was to determine the effects of aducanumab on cognition in AD patients using the CDR-SB. Other tools used to measure patients' cognitive decline were MMSE, the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), and the Alzheimer's Disease Assessment Scale-cognition sub-scale 13 (ADAS-cog13). Biomarkers of AD were also analyzed in central spinal fluid, and PET scans were obtained to analyze the effects of aducanumab on Aβ and tau proteins.[46]

After post hoc analysis, both the *Emerge* and *Engage* trials demonstrated that high-dose aducanumab reduced the total number or size of Aβ plaques in patients relative to placebo.[47,48] Patients who received low-dose aducanumab experienced a reduction in PET SUVR of 0.165 and 0.168 in the *Emerge* and *Engage* trials, respectively ($P < 0.001$).[49] Patients who received high-dose aducanumab experienced a reduction in PET SUVR of 0.272 and 0.238 in the *Emerge* and *Engage* trials, respectively ($P < 0.001$).[46,49] Compared to other monoclonal antibodies (solanezumab, bapinezumab, gantenerumab), aducanumab is the only monoclonal anti-Aβ antibody developed that has been shown to significantly reduce Aβ PET SUVR in phase III clinical trials.[47]

Post hoc analysis of the *Emerge* trial indicates high-dose aducanumab may reduce the rate of functional and cognitive decline in patients with mild AD.[46–49] Results from *Emerge* show aducanumab improved AD patients' scores on metrics of cognitive and physical function including the neuropsychiatric inventory (NPI), CDR-SB, ADAS-Cog13, and ADCS-ADL.[47,50] *Emerge* trial patients showed an average 87% decrease from baseline on the NPI, and their caregivers reported an 84% decrease in distress. Of those who completed the *Emerge* trial, patients who received a placebo experienced a 22% greater decrease in CDR-SB relative to participants who received high-dose aducanumab. Furthermore, *Emerge* and *Engage* patients that received at least 14 doses of high-dose aducanumab showed average delays in lowering of CDR-SB by 30% and 27%, respectively.[50] Aducanumab was also found to significantly improve scores in ADAS-Cog13. However, it did not improve MMSE with statistical significance.[47] All patients receiving aducanumab experienced an average 40% mitigation of loss of ability to carry out daily living relative to patients receiving placebo, according to ADCS-ADL scores.[50]

SKEPTICISM SURROUNDING ADUCANUMAB'S EFFICACY

A major concern regarding aducanumab's phase III clinical trials is both were halted roughly halfway in March 2019 because of failure to significantly improve AD symptoms.[49] Neither *Engage* nor *Emerge* showed significant improvement in patients' CDR-SB scores, and each study's findings met pre-determined futility criteria.[48,49,51] However, months later more participants finished each trial, and supplementary data from these patients made it such that *Emerge* patients experienced significant benefit from aducanumab treatment according to CDR-SB scores. The high-dose group in the *Emerge* trial met its primary goal and established significance after the data was supplemented ($P = 0.01$).[52] After post hoc analysis, *Engage* still did not meet primary outcomes.[48,49] Possible confounding variables identified for the *Engage* trial include fewer individuals who received high-dose aducanumab and increased number of outliers who experienced dramatic worsening of symptoms.[51] The incongruence of these studies after post hoc analysis has sparked debate as to the drug's efficacy with some calling for further clinical trials. In November 2020, an FDA advisory committee perceived that the *Emerge* and *Engage* trials did not provide strong evidence that aducanumab has shown effectiveness in the treatment of AD.[51,52]

Another concern is that the benefit in cognitive function observed in patients from the *Emerge* trial may not be clinically significant. A 2019 study established that for treatment for AD to reach clinical significance, it must show an average difference of at least 1 point in CDR-SB for MCI patients and 2 points for patients with mild AD.[53] Based on data released by Biogen on October 22, 2019, the results from high-dose groups in both *Emerge* and *Engage* did not reach a 1 point difference.[48] Also, aducanumab had significant improvement of CDR-SB and ADCS-ADL scores, but these improvements had effect sizes of < 0.2 indicating minor clinical changes.[47] These improvements do indicate that aducanumab could enhance both cognition and daily living in patients with MCI or mild AD. However, the magnitude of this drug's benefit may only be statistically significant and not clinically significant.[51–53]

PATIENT SAFETY

In clinical trials, aducanumab has been associated with various side effects. The most common side effects reported include headache, diarrhea, and other constitutional symptoms.[35,44,47] One of the most severe major side effects of all anti-Aβ monoclonal antibody therapies, including aducanumab, is ARIA-E.[45–47] A meta-analysis by Avgerinos et al[47] determined that among 3 other anti-Aβ antibody immunotherapies, aducanumab is associated with the greatest risk of developing ARIA-E. Notably, although there have been deaths associated with other anti-Aβ immunotherapy treatments such as bapinezumab and solanezumab, there have been no deaths associated with the use of aducanumab to treat AD.[44–46]

CONCLUSION

Pre-clinical studies and clinical trials have suggested the ability of aducanumab to restore neurological function in patients with AD by reducing Aß plaques and reestablishing neuronal calcium permeability.[42,43] However, discrepancies in post hoc analysis findings have cast doubt on the research and medical community. Some studies suggest the benefits of aducanumab are perhaps limited to statistical significance and lack clinical significance.[51–53] In contrast, other studies argue the FDA vote for the denial of aducanumab stemmed from a narrow perspective failing to take other aspects into consideration.[50] While it's possible confounding variables played a role in the difference seen between the *Emerge* and *Engage* trials, the observed incongruency has emphasized the need for repeated trials to increase confidence.[51] Despite the persistent skepticism in clinical efficacy, aducanumab has proven to significantly decrease amyloid in all cortical brain regions examined.[34,35] In summary, aducanumab has provided hope for those working toward the goal of providing patients a potentially safe and viable treatment option in the management of AD.

DEDICATION

This review is dedicated to you, Dr. J.G. MD and to the memory of your beloved grandfather Z''L.

AUTHOR CONTRIBUTIONS

Hannah W. Haddad, Garett W. Malone and Nicholas J. Comardelle typed the bulk of the paper. Arielle E. Degueure and Salomon Poliwoda revised the references and made editions to the paper. Rachel J. Kaye, Kevin S. Murnane, Adam M. Kaye and Alan D. Kaye gave their intellectual input.

CONFLICTS OF INTEREST

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Table 1. Clinical Efficacy and Safety

Author (Year)	Purpose and Intervention	Results and Findings	Conclusions
Alexander et al[52] (2021)	The efficacy of aducanumab for the treatment of AD is evaluated using outcomes from aducanumab's phase I and phase III clinical trials.	After supplementary data was incorporated following phase III trials being halted, *Emerge* met its primary goal ($P = 0.01$). An FDA advisory committee voted by majority that results from *Emerge* and *Engage* failed to demonstrate that aducanumab deserved FDA approval. The post hoc analyses for *Engage* and *Emerge* increase the likelihood of introduction of bias into data review and interpretation.	Data from *Emerge* and *Engage* may not provide enough evidence to support FDA approval of aducanumab to outweigh the fact that both trials were halted for evidence of futility.
Avgerinos et al[47] (2021)	This meta-analysis and systematic review evaluated the risks and benefits associated with phase III clinical trials using monoclonal anti-Aß antibodies for the treatment of AD. Data from 17 studies (2 on gantenerumab, 3 on solanezumab, 6 on bapineuzumab, and 4 on aducanumab) involving 12 phase III clinical trials are included.	Aducanumab was found to have the greatest risk of ARIA-E of any anti-Aß immunotherapeutic antibody developed. Aducanumab is the only monoclonal anti-Aß antibody that has been found to significantly reduce Aß PET SUVR ($P < 0.05$). Aducanumab improved patient CDR-SB and ADCS-ADL scores with an effect size of < 0.2.	Aducanumab showed the most benefit in treating AD pathology and symptoms among the anti-Aß antibodies available based on biomarker and clinical symptom improvement.
Cummings et al[50] (2021)	Data from aducanumab's Phase III *Engage* and *Emerge* trials are compared to findings from other phase III AD-modifying monoclonal antibody drug trials.	Patients receiving high-dose aducanumab in the *Emerge* trial experienced an 87% decrease from baseline in NPI. High-dose patients in the *Emerge* trial also experienced a ~40% improvement in ADCS-ADL score relative to placebo patients. Trials for other anti-Aß monoclonal antibodies for the treatment of AD have shown dose-dependent effects like the pattern observed in the *Emerge* trial.	The *Emerge* trial demonstrated clinical benefit in the treatment of AD, and its findings are supported by findings in similar studies.
Knopman et al[49] (2021)	The significance of findings from *Engage* and *Emerge* are evaluated.	Both *Emerge* and *Engage* showed a dose-dependent reduction in size of Aß plaques relative to placebo based on PET SUVR ($P < 0.001$). After post-hoc analysis, *Emerge* met its primary target in reducing cognitive decline while *Engage* did not.	Another Phase III clinical trial may be necessary to confirm the efficacy of high-dose aducanumab demonstrated in the *Emerge* trial.
Kuller and Lopez[51] (2021)	The validity of findings from *Engage* and *Emerge* is determined. Further steps in verification of aducanumab as a therapy for AD are examined.	*Emerge* is the first phase III clinical trial where an anti-Aß monoclonal antibody immunotherapy has been able to show slowing of cognitive impairment in patients suffering from AD or MCI. Possible confounding variables in *Engage* were identified including a lower number of high-dose patients and the presence of outliers.	Patients from the *Engage* and *Emerge* trials should be evaluated long-term to observe the effects of aducanumab. Another phase III clinical trial using high-dose aducanumab is warranted.
Howard and Liu[48] (2020)	The validity of interpretations from phase I and phase III trials regarding aducanumab for the treatment of AD is analyzed.	To show significant clinical benefit, AD treatment must show an average difference in CDR-SB score of 1 point for patients with MCI and 2 points for patients with mild AD. Neither high-dose group from *Engage* nor *Emerge* reached a 1-point difference from placebo patients. Aducanumab's efficacy at degrading Aß plaques was supported in both phase III trials.	Phase III clinical trials for aducanumab did not show clinically significant benefit for AD patients in terms of CDR-SB score.
Tian Hui Kwan et al[46] (2020)	Findings from multiple Aß-targeted monoclonal antibody therapies that entered phase III clinical trials are	Aducanumab was found to have positive dose-dependent clinical benefit in its Phase Ib study. Data from high-dose aducanumab	Aducanumab's *Engage* and *Emerge* trials show

Author (Year)	Purpose and Intervention	Results and Findings	Conclusions
	compared. These drug therapies include crenezumab, gantenerumab, solanezumab, and aducanumab.	patients in the *Emerge* and *Engage* trials showed an average improvement in CDR-SB of 23% ($P = 0.010$) and -2% ($P = 0.825$) respectively. The average score improvement in CDR-SB observed in patients in the *Emerge* trial was by a score of 0.4 points on an 18-point scale.	conflicting results, and the *Emerge* trial's findings may be of little clinical significance.
Mo et al[45] (2017)	This meta-analysis and systemic review evaluates the safety and efficacy of monoclonal anti-Aß antibodies for the treatment of AD.	ARIA-E was one of the most reported side effects, but no deaths were reported in the Phase Ib clinical trial for aducanumab. Aducanumab significantly improved MMSE scores in patients with MCI or mild AD relative to placebo in the *Prime* trial. Aducanumab was not found to significantly improve patients' DAD or ADAS-cog13 scores.	Aducanumab's phase Ib clinical trial showed that aducanumab may help prevent cognitive decline in AD patients and significantly increase one's risk of developing ARIA-E.
Gamage and Kumar[43] (2017)	The role of calcium dysregulation in neurodegenerative disorders, such as AD, and how aducanumab may alter dysfunction.	Aß plaques increase the clearance of NMDA receptors from neurons' cell surfaces, which contributes to disruption in Ca^{2+} permeability. Aducanumab has been able to decrease Aß plaque size in human and mouse trials. Aducanumab was found to significantly recover SERCA pump regulation which was disrupted in transgenic mice with Aß plaques ($P < 0.001$).	Aducanumab may improve neurological function in patients with neurodegenerative diseases caused by Aß plaques by restoring function of NMDA receptors and SERCA pumps.
Kastanenka et al[42] (2016)	Transgenic mice overexpressing amyloid precursor protein were grown and treated acutely with topical administration of an aducanumab analog directly to the brain (0.42-1 mg/ml) or were treated weekly with 10 mg/kg aducanumab for 6 months. Each mouse's brain was imaged using fluorescent microscopy to tag Aß plaques, and biomarkers were measured before and after treatment.	Acute topical treatment with aducanumab analog significantly reduced the number of Aß plaques at a greater rate than the reduction observed in control mice ($P < 0.0001$). Chronic treatment with aducanumab analog did not show significant reduction in the number of Aß plaques ($P = 0.35$). Mice that received chronic treatment had a lower incidence of calcium overload ($P < 0.05$) and increased calcium permeability relative to controls ($P < 0.05$).	Aducanumab may decrease the rate of cognitive decline in AD patients not only by degradation of Aß plaques but by re-establishing physiological intracellular calcium levels.
Ferrero et al[44] (2016)	Aducanumab was studied in a single-dose-escalation, placebo-controlled, randomized, double-blind phase I clinical study. This study included 53 patients with mild or moderate AD who received placebo or 0.3, 1, 3, 10, 20, 30, or 60 mg/kg doses of aducanumab and were followed up to 24 weeks after receiving treatment.	All 3 patients who received 60 mg/kg of aducanumab developed ARIA-E which ultimately resolved. Pharmacokinetic findings indicated that increasing dosage did not alter the rate of clearance, half-life, or volume of distribution of aducanumab. ARIA-E was the most severe adverse effect observed, with most other adverse effects being constitutional complaints.	The only observed severe adverse effect in this study was ARIA-E which has been associated with other monoclonal anti-Aß antibody immunotherapies.
Sevigny et al[35] (2016)	Aducanumab was studied in a placebo-controlled, randomized, double-blind phase Ib trial including 165 patients. These participants with MCI or mild AD were administered 1, 3, 6, or 10 mg/kg of aducanumab monthly for 12 months.	Aducanumab reduced cognitive decline in AD patients that received 3 or 10 mg/kg of aducanumab based on MMSE ($P < 0.05$). 41% of participants receiving 10 mg/kg aducanumab developed ARIA-E. PET SUVR score was lowered relative to baseline in patients that received 10, 6, and 3 mg/kg of aducanumab ($P < 0.001$).	Aducanumab sufficiently crosses the BBB to aid in the degradation of Aß plaques in a dose-dependent manner in AD patients.

Key: Alzheimer's Disease (AD); Food and Drug Administration (FDA); beta-amyloid (Aβ); Alzheimer's related imaging abnormality-edema/effusion (ARIA-E); Positron Emission Tomography (PET); standard uptake volume ratio (SUVR); Clinical Dementia Rating Scale-sum of boxes (CDR-SB); Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL); neuropsychiatric inventory (NPI); mild cognitive impairment (MCI); mini mental state examination (MMSE); disability assessment for dementia (DAD); Alzheimer's Disease assessment scale-cognitive subscale 13 (ADAS-cog13); N-methyl-D-aspartate (NMDA; sarcoendoplasmic reticulum calcium ATPase (SERCA); blood brain barrier (BBB)

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