Alzheimer's Dementia

Dong Kyu (Samuel) Shin, PhD, Carolina Osorio, MD, David Puder, MD

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Why is this important for mental health professionals?
Alzheimer's disease is a devastating neurodegenerative condition that affects the entire family. As psychiatrists and psychologists, we often support these patients and their families throughout this entire disease process. With the recent and controversial FDA approval of aducanumab (Aduhelm™), a new pharmacotherapy for Alzheimer's disease, we can expect to be asked about this drug from our patients and their family.

Initially, there was a lot of excitement from the scientific community when aducanumab and other similar pharmacotherapies first entered clinical trials. However, phase III clinical trials of several drugs in this class failed to show clinical improvement in memory and cognitive functions, despite their high efficacy in removing the CNS amyloid plaques, the classic brain pathology of Alzheimer's disease. Therefore, it was a surprise to many scientists and clinicians when FDA officially approved aducanumab on June 7th, 2021.

When we took a deep dive into the controversy, our findings were shocking. Not only is the new therapy aducanumab (Aduhelm™) not effective in providing clinical benefits in memory and cognitive functions, it is also associated with adverse side effects that we need to be ready to discuss in detail when the opportunity arises. Furthermore, the entire FDA review and approval process of aducanumab, as well as its high price tag, is now under investigation by the Office of the Inspector General (OIG) of the Department of Health and Human Services (HHS) and congressional committees (Rubin, 2021).

What is Alzheimer's disease?
Alzheimer's disease (AD) is a progressive and fatal neurodegenerative condition with no cure. Today, AD affects more than six million Americans and their families (Alzheimer's Association). That is 1 in 9 adults older than 65 years of age. For more than ninety percent of patients with AD, the symptoms usually develop in the late adulthood in their 60s and 70s (Barber, 2012). A very small portion of patients (<5%) have what is called an accelerated or familial Alzheimer's, which can present as early as late 40s to early 50s (Barber, 2012). Memory complaint is often the most common first symptom, but other early signs of AD include difficulty with problem solving, completing familiar tasks, understanding visual images (such as road signs), withdrawal from work or social activities, and changes in mood or personality (Alzheimer's Association).

As the disease progresses, the instrumental activities of living (IADLs) are the first to go. These include managing finances, managing transportations, shopping, meal preparation, home maintenance, housekeeping, and managing medications. In the late stage of AD, activities of daily living (ADLs) become severely compromised. ADLs include walking, feeding, dressing, grooming, toileting, bathing, and transferring. These patients can no longer take care of themselves in the most basic way and often wander and get lost. Additionally, late-stage AD patients often suffer from difficulty in swallowing (resulting in frequent aspiration pneumonias), as well as urinary and fecal incontinence. Therefore, late-stage AD usually requires skilled nursing facilities or even a higher level of care.

Given the high prevalence and the insidious and chronic natural course of the disease, it is not surprising that AD takes up a large portion of our nation's healthcare spending. This year (2021) alone, AD will cost our nation 355 billion dollars in healthcare spending (~$59,000 per patient), and that number is expected to go up to 1.1 trillion dollars by 2050 (Alzheimer's Association). AD also creates a heavy burden on the family members. In 2020, more than 11 million people provided UNPAID care for people with AD, an estimated 15.3 billion hours of care valued at nearly 257 billion dollars (Alzheimer's Association). To put this in perspective, the entire U.S. Medicare spending in 2019 was reported as 799 billion dollars and U.S. Medicaid spending in 2019 was 613 billion dollars (National Health Expenditures 2019 Highlights).

How do you diagnose Alzheimer's disease?
AD is a clinical diagnosis, meaning it is diagnosed based on history findings and clinical testing. Today, AD diagnosis is often made by psychiatrists, clinical psychologists, primary care physicians, and neurologists. Diagnosis usually involves a single or series of cognitive testing as well as laboratory work up and imaging to rule out other causes of cognitive impairment (hypothyroidism, vitamin deficiencies, tumors, vascular dementia, TBI, etc.). There is no biochemical test for AD although blood and CSF markers are actively being researched (Waldemar et al., 2007).

Commonly used cognitive tests are the Mini-Mental State Exam (MMSE), Clinical Dementia Rating Scale (CDR), and Montreal Cognitive Assessment (MoCA). Other commonly used tests include Alzheimer's Disease Assessment Scale–Cognitive Subscale-13 (ADAS-Cog13) for cognition, Alzheimer's Disease Cooperative Study–Activities for Daily Living Inventory (ADCS-ADL) for functional assessment, and Neuropsychiatric Index (NPI) for behavioral assessment (Nasreddine et al., 2005; Waldemar et al., 2007). For early-stage patients whose cognitive impairment symptoms are not as overt, clinical neuropsychologists can administer a battery of cognitive and functional testing to make the diagnosis of mild-cognitive impairment (MCI).

What are the treatments for Alzheimer's disease?
Currently, there are only four FDA-approved pharmacotherapies for AD. However, their overall efficacy in preventing or slowing the progression of neurodegeneration in AD is minimal (Waldemar et al., 2007; Yiannopoulou & Papageorgiou, 2020).

We hint at things that can make an impact, including exercise, diet, and sleep, which although there might not be any money to promote and might be very difficult to change, can make a huge impact.

Current FDA-approved pharmacotherapies for Alzheimer's disease?
Mild-moderate AD: Central acetylcholinesterase inhibitors

- Donepezil (Aricept), FDA-approved in 1996
- Rivastigmine (Exelon), FDA-approved in 1998
- Galantamine (Razadyne), FDA-approved in 2001

Moderate-severe AD: NMDA-R antagonist

- Memantine (Namenda), FDA-approved in 2003

Amyloid hypothesis and its role in Alzheimer's disease therapeutic development
In 1907, Dr. Alois Alzheimer first described the neuropathological findings of a 51-year-old woman who died from an advanced dementia syndrome (Strassnig & Ganguli, 2005). In his histology slides of the post mortem brain, he was the first one to show the presence of thick and darkly-staining extracellular plaques, as well as darkly-staining intracellular "clumps" or "tangles" inside the neurons. From there, however, no real advance in research was made until the 1980s when these plaques and tangles were characterized biochemically. In 1984, the extracellular plaques were found to be an aggregation of amyloid beta protein (Glenner & Wong, 1984) and in 1986, the intracellular tangles were characterized as hyperphosphorylated tau proteins (Wolozin et al., 1986).

In 1992, two scientists proposed a hypothesis called the "amyloid hypothesis" of AD based on pathological findings of some post mortem AD brains, namely amyloid beta plaques and tau neurofibrillary tangles (Hardy & Higgins, 1992). This hypothesis proposed that abnormal accumulation of amyloid beta protein is the initiating step of a pathogenic cascade that leads to neurofibrillary tangles of tau in the neurons and neuronal death.

Based on this hypothesis, the authors of this work also proposed a prediction that creating a pharmacotherapy that can prevent or remove amyloid beta proteins from the brain will cure AD (Hardy & Higgins, 1992). For the past three decades, hundreds of amyloid-targeting therapies were developed and underwent clinical trials. Between 2002-2012, there were over 400 clinical trials looking at amyloid-targeting compounds (Fernández, 2020). Today, in 2021, there are 126 AD therapies being studied in 152 clinical trials, most of them directly targeting the amyloid beta protein (Cummings et al., 2021). However, every single one of these drugs have failed to show clinical efficacy in treating the symptoms of AD (memory and cognitive function) and none of these medications have been approved by the FDA (Fernández, 2020; Cummings et al., 2021).

In the early 2000s and on, amyloid therapies for AD began to shift towards biologics, namely monoclonal antibodies. This type of therapy utilized the body's natural immune system to clear amyloid tagged by the "designer amyloid antibodies." The new FDA-approved drug aducanumab (Aduhelm™) falls into this

category. Many pharmaceuticals have pursued this option (i.e., solanezumab by Eli Lilly and Co., bapineuzumab by Pfizer and Jassen, gantenerumab by Roche, aducanumab by Biogen). Many clinical trials of these drugs showed successful clearance of amyloid plaques and deposits from the brain (Castello et al., 2014). However, none of the phase III clinical trials of these drugs were able to show clinical benefits in memory or cognitive function and did not reach the FDA-approval, until aducanumab.

What is aducanumab? How does it work? How is it given?
Aducanumab (brand name Aduhelm™) by Biogen Inc. is a human IgG1 monoclonal antibody against human amyloid beta protein (Alexander et al., 2021; Sevigny et al., 2016). It falls under the biologic category, meaning the drug contains some direct biological component such as proteins or genetic material (DNA/RNA). Aducanumab is designed to be delivered intravenously over an hour-long infusion at an infusion center. According to Biogen Inc., aducanumab is designed to be delivered over fourteen infusions given every four weeks. To monitor for adverse effects, several MRIs are indicated, including the baseline MRI prior to initiating therapy and routine surveillance MRIs throughout the course of the 14-month treatment.

What is the controversy?
When patients hear about various controversies in medicine, they may often assume that the controversy is based on minor differences in opinions. And often this is true, especially when it comes to clinical management of a complicated disease process that requires a nuanced approach to maximize clinical benefits. This is where clinical acumen and experience plays a role in making decisions, not just a cookie-cutter flowchart or protocol that clearly defines an algorithm. When it comes to understanding the controversy surrounding aducanumab, it is imperative that we have a clear understanding of the scientific evidence to properly guide our conversations with our patients.

From early on, there was strong evidence that aducanumab, as well as several other similar biologics from other companies, had no problem demonstrating their high efficacy in clearing amyloid plaques from the brain. However, phase III trials of various amyloid-targeting biologics (including aducanumab) were not able to improve memory and cognitive function (Castello et al., 2014; Knopman et al., 2021), perplexing many scientists and business investors in the neuroscience sectors of major pharmaceuticals.

In March of 2019, Biogen itself halted its phase III clinical trials of aducanumab following an internal futility analysis (it is a common practice to do a futility analysis halfway through an expensive trial to determine if the data trend justifies further financial investments into the trials) (Knopman et al., 2021). On March 21, 2019, Biogen announced these results and closed the trials, resulting in an estimated 15- to 18-billion-dollar loss for the company (News/News). It is important to note that several other major pharmaceuticals also closed their trials for similar reasons. Since then, Pfizer famously went as far as to completely shut down its neuroscience sector (News).

Nevertheless, Biogen did not give up. Between March of 2019 and July 2020, Biogen conducted several reanalyses of their data, created long and confusing justifications for their failed arm of the study, and resubmitted to the FDA in July 2020 (Combined FDA and Biogen briefing information). For reasons that are not well understood (and currently under investigation), the FDA quickly accepted this second application and granted priority review (Combined FDA and Biogen briefing information). In November 2020, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted against recommending the drug based on the lack of clinical efficacy (Alexander et al., 2021). However, the FDA officials formally approved aducanumab under the accelerated track despite the lack of evidence.

There are several layers to the aducanumab controversy. The first is the fact that the FDA approved the drug against its own review committee. Every member of the Peripheral and Central Nervous System Drug Advisory Committee (comprised of independent experts not associated with Biogen) that reviewed Biogen's aducanumab application voted against the drug. Nevertheless, in an unprecedented event, high-ranking FDA officials supported this drug and approved it against the committee decision. Since this approval, three of the committee members have resigned (Joel Perlmutter, MD, Neurologist, Washington University; David Knopman, MD, Neurologist, Mayo Clinic; Aaron Kesselheim, MD, JD, MPH, Harvard Medical School) (News).

The next area of concern is the close partnership between the FDA and Biogen. Dr. Billy Dunn, the director of FDA Office of Neuroscience has been accused of having regular informal meetings with top Biogen officials (Dr. Alfred Sandrock, Executive VP of R&D and Samantha Budd Haeberlein, Head of Neurodegeneration Development Unit) (News). Dr. Janet Woodcock, the interim commissioner of the FDA has recently requested a formal investigation from the Office of Inspector General at the U.S. Department of Health and Human Services (Rubin, 2021).

Third, the high cost of this drug and its implication for profit for Biogen has created a lot of controversy, especially in the political realm, as a large portion of this medication is expected to be paid by the taxpayers. The drug is priced at $56,000 per year, not including the infusion center cost, routine MRIs, and hospitalizations associated with common adverse effects of aducanumab. While Biogen has publicly justified the cost of aducanumab by making comparisons to biologics used for cancer treatments (News), the financial implication of this medication remains a huge challenge for our nation's healthcare spending.

Lastly, there is controversy over the risk versus benefit of aducanumab, given the high incidence of severe adverse reactions, namely ARIA-Edema and ARIA-H microhemorrhage. Given virtually no significant clinical benefit but up to 43% chance of developing brain edema or brain hemorrhage (Combined FDA and Biogen briefing information), physicians must facilitate the risk vs. benefit conversation of aducanumab treatment.

A deeper dive into the clinical data presented by Biogen to the FDA

For those who are interested, all the official data, presentations, rosters, meeting minutes, and more are publicly available on the FDA's website.

In summary, Biogen conducted a total of six clinical studies on aducanumab. The first four were phase I and II trials with small numbers of patients to generate pilot data, dose-response curves, and to conduct basic safety analysis. Next, they moved on to two parallel phase III studies named 301 ENGAGE and 302 EMERGE. The primary endpoint of the studies was defined as significant improvement in the Clinical Dementia Rating sum-of-boxes.

As mentioned above, Biogen's futility analysis showed no significant change in clinical outcome. Both 301 and 302 showed efficient removal of amyloid. However, while 302 EMERGE trended towards ~1 point improvement in the primary endpoint, the 301 ENGAGE trial showed an opposite effect: ~1 point worsening in the primary endpoint. Given the near equal number of patients (~1,600 each), the average of the two showed near zero improvement in improving memory or cognitive function.

Biogen's justification of their failed results to the FDA is quite stunning. In a nutshell, Biogen claimed that the results from the 302 study, which showed improvement, should be enough to get the drug approved. For the 301 study that showed worsening of clinical symptoms, Biogen claimed that this study had 4 more outliers than the 302 that ruined the trend of the entire study. Biogen then claimed that their reanalysis justifies dropping this entire arm of the phase III study consisting of more than 1,600 patients. Clearly, the FDA review committee did not agree with this claim, which resulted in unanimous voting against this drug's approval. (It is important to note that Biogen's data trend does not change even after they selectively removed the outliers from all studies and reanalyzed their data.)

The aftermath

Prior to and since aducanumab's approval, several scientific and clinical experts have spoken out against the FDA approval of aducanumab. Many major hospital systems and universities have also stated their positions against this approval, including the Cleveland clinic, Mount Sinai, and Providence. Several medical societies have also stated their position on FDA's aducanumab approval.

American Geriatric Society's letter to the FDA commissioner, requesting to not approve aducanumab based on the lack of scientific evidence.

American Association of Geriatric Psychiatry (AAGP) Statement on Aducanumab following the FDA approval.

American Neurological Association (ANA) Statement on Aducanumab following the FDA approval.

Adverse effects of aducanumab

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There are two severe adverse effects of aducanumab, known as Amyloid-related imaging abnormalities-Edema and -Hemorrhage (ARIA-E and ARIA-H). We believe that ARIA is a terminology that makes it sound rather harmless when in reality, ARIA-E is a widespread vasogenic edema caused by aducanumab therapy, and ARIA-H is micro- or macro-hemorrhages caused by aducanumab therapy (Sperling et al., 2011). Please refer to the full Biogen presentation for the complete data on aducanumab's adverse effects.

ARIA-E:
Based on Biogen's data to the FDA, there were three doses of aducanumab in the treatment arm (3, 6, and 10 mg/kg) and the incidence of ARIA-E in the treatment group ranged from 20.5% up to 35.0% depending on the dosing. In comparison, the incidence of ARIA-E in the placebo group was 2.7%. It is important to highlight that in the aducanumab arm of the study, the incidence of ARIA-E was doubled in patients with ApoE ε4 carriers (43.0%) compared to the non-carriers (20.3%). The ApoE gene has 3 different alleles: ε2, ε3, and ε4. People with the ε4 allele of ApoE have been identified to be at significantly higher risk of developing AD (Barber, 2012; Corder et al., 1993).

ARIA-H:
Based on Biogen's data to the FDA, patients who received 10 mg/kg of aducanumab had 19.1% incidence of ARIA-H compared to the 6.5% in the placebo arm. It is important to mention that patients with any level of amyloid accumulation in the brain are already at risk for hemorrhage due to a pathologic process called cerebral amyloid angiopathy, in which amyloid plaques compromise the integrity of cerebral vasculature (Jäkel et al., 2021), which may explain the 6.5% incidence of ARIA-H in the placebo group. It is important to note that removal of these plaques resulted in the increased incidence of brain bleeds while providing no benefits in memory and cognitive function.

Aducanumab take-home points:

- Aducanumab is a biologic, a human IgG1 antibody against CNS beta-amyloid plaques.
- Aducanumab is administered intravenously at an infusion center q1mo.
- Aducanumab costs $56,000 per year + infusion cost + surveillance MRI cost + radiology + ARIA treatment.
- Aducanumab was approved by the FDA against FDA's independent expert panel.
- Aducanumab's clinical efficacy is questionable, with two conflicting phase III trials that showed exact opposite results that average out to near zero in clinical efficacy.
- Under the best scenario, aducanumab appears to improve CDR-SB by ~1 pt after 1+ year of therapy.
- Aducanumab is associated with significant adverse effects of ARIA-E and ARIA-H.
- ~35% patients will develop ARIA-E and that goes up to ~43% if ApoE ε4 carrier.
- ~20% of patients will develop ARIA-H.
- Patients with amyloid plaques are already at increased risk of hemorrhage (due to Cerebral Amyloid Angiopathy). Aducanumab increases this risk.

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Why do amyloid-targeting therapies not work? Maybe not all Alzheimer's are the same!
Since the emergence of the amyloid hypothesis, Alzheimer's disease has been taught and researched as a single disease: a disease caused by aberrant amyloid biology. In reality, however, there are at least three types of AD (Barber, 2012):

1. **Familial or early-onset AD (FAD, < 5% of AD patients):**
   This group of patients *do* carry genetic mutations in genes that are directly involved in amyloid processing, such as amyloid precursor protein or amyloid cleaving proteins such as PSEN1 and PSEN2 (Barber, 2012). FAD patients also present with memory and cognitive symptoms as early as their 30s to 40s. The first AD patient described by Dr. Alois Alzheimer likely falls under this group. Almost all of the basic science research in AD has been carried out under this genetic model of AD despite the low prevalence of this type of AD in the patient population (Castello et al., 2014; Castello & Soriano, 2014).

2. **AD associated with trisomy 21 Down syndrome:**
   This is technically a subgroup of familial AD in that it is caused by an extra copy of the APP gene which is located on chromosome 21 (Barber, 2012). Down syndrome patients often develop AD symptoms as early as in their 40s (Barber, 2012).

3. **Sporadic or late-onset AD (SAD, > 90% patients):**
   More than 90% of AD patients develop the disease sporadically in late-adulthood (Barber, 2012). These patients do not have genetic mutations that are directly related to amyloid generation or clearance (Barber, 2012). Rather, the genetic mutations or other epigenetic risk factors of SAD are quite broad, ranging from genes related to cholesterol metabolism to inflammation and immune response (Barber, 2012; Carmona et al., 2018; Van Cauwenberghe et al., 2016; Yamazaki et al., 2019). Epigenetic risk factors (caused by lifestyle choices or other comorbidities) include chronic inflammation, dyslipidemia, insulin resistance, and psychiatric comorbidities such as depression, anxiety, post traumatic stress disorder, and chronic sleep disturbance (Becker et al., 2018; Bredesen, 2015; Castello & Soriano, 2013; Delic et al., 2021; Diniz et al., 2013; Ferreira et al., 2018; Torres-Berrio & Nava-Mesa, 2019; Watson & Craft, 2003). Further research is needed to better classify this majority population of AD.

Connect with Dr. Osorio: here

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