Medical News & Perspectives

Recently Approved Alzheimer Drug Raises Questions That Might Never Be Answered

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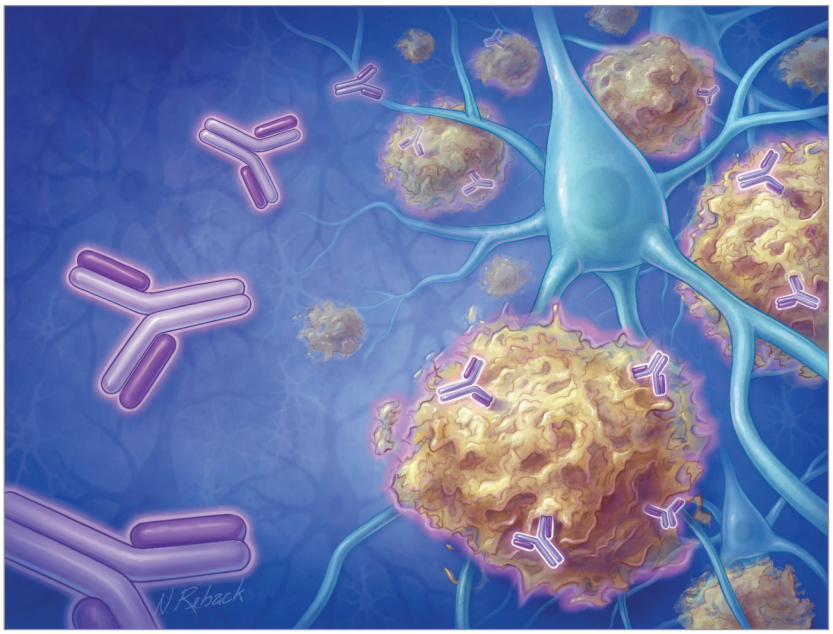
The Food and Drug Administration's (FDA's) approval June 7 of the drug aducanumab was notable for a number of reasons:

- It was the first time the FDA had approved an Alzheimer disease medication in 18 years, and the first time ever that the agency had approved a drug designed to target the underlying disease process.
- It bucked the opinion of the FDA's panel of outside experts, none of whom voted "yes" last November when asked whether clinical trials had shown aducanumab to be effective in treating Alzheimer disease. Three committee members resigned in response to the agency's decision; one called it "probably the worst drug approval decision in recent US history."
- It moved a US senator to ask President Joe Biden to replace FDA Acting Commissioner Janet Woodcock, MD, with a permanent commissioner.
- It drove Woodcock to ask the Office of the Inspector General of the US Department of Health and Human Services (HHS) to conduct an independent review of her own agency's inner workings, specifically "interactions between representatives of [manufacturer] Biogen and the FDA during the process leading to" aducanumab's approval.
- It spurred the chairs of 2 US House of Representatives committees to announce that they would investigate the process that led to the drug's approval and its $56 000-a-year price tag.
- And it has left dementia specialists debating about which patients, if any, might benefit from aducanumab.

Neurologist Allan Levey, MD, PhD, director of Emory University's Goizueta Alzheimer Disease Research Center, was blunt in his assessment of aducanumab, sold under the brand name Aduhelm and marketed by Biogen, based in Cambridge, Massachusetts, and Eisai, headquartered in Tokyo.

"I would not have approved it," Levey, who is not a member of the FDA advisory committee that reviewed aducanumab, said in an interview. "I think the scientific question of whether it works is still open."



Despite the controversial approval of aducanumab, an antiamyloid monoclonal antibody for people with mild Alzheimer disease, the role that amyloid-β accumulation plays in clinical symptoms is still up for debate.

But the FDA didn't base its decision on whether aducanumab worked to slow cognitive decline in patients with Alzheimer disease when it approved the drug. Instead, after the advisory committee concluded that placebo-controlled trials failed to clearly show aducanumab was effective in treating the disease, the FDA mapped out a shortcut to approval for the drug.

The agency granted "accelerated approval" to aducanumab, a pathway for "earlier approval of drugs that treat serious conditions and that fill an unmet medical need based on a surrogate endpoint," as the FDA describes it. A condition of accelerated approval is that manufacturers conduct postapproval, or phase 4, clinical trials to see whether meeting the surrogate end point provides the anticipated clinical benefit.

"The data included in the applicant's submission were highly complex and left residual uncertainties regarding clinical benefit," Patrizia Cavazzoni, MD, director of the FDA's Center for Drug Evaluation and Research (CDER) acknowledged in a prepared statement after the approval.

Aducanumab is an antiamyloid monoclonal antibody, administered as an intravenous infusion every 4 weeks. A surrogate end point used in the phase 3 trials was the level of amyloid-β plaques—protein clumps that are a hallmark of Alzheimer disease—in participants' brains. Higher levels of amyloid plaques, detected via positron emission tomographic (PET) scans or on autopsy, are associated with more advanced Alzheimer disease, although some people with amyloid plaques in their brain never experience impaired cognition.

Clinical trials showed that aducanumab was effective in removing amyloid plaques. However, although biomarkers such as amyloid-β may be useful in precisely diagnosing the disease and predicting its clinical course, they don't

predict the clinical efficacy of drugs designed to treat it, researchers from an Italian pharmaceutical company concluded in an article last November.

The "Amyloid Hypothesis"

In an article 30 years ago, 2 scientists from the biochemistry and molecular genetics department at London's St Mary's Hospital Medical School proposed that amyloid deposition in the brain was the "central event in the etiology of Alzheimer's disease." Understanding this "pathological cascade" would facilitate rational drug design to intervene in the process, John Hardy, PhD, and David Allsop, PhD, wrote.

The hunt for drugs that could reduce amyloid plaques was on.

"People are attached to this idea: The amyloid hypothesis must be true, and if you remove amyloid, you must be treating Alzheimer's disease," Lon Schneider, MD, professor of psychiatry, neurology, and gerontology at the University of Southern California's Keck School of Medicine and director of the California Alzheimer Disease Center, told *JAMA*.

But, as Michael Carome, MD, testified before the FDA advisory committee, 22 other drugs targeting amyloid-β accumulation, including 5 other antiamyloid-β monoclonal antibodies, have failed to show clinical benefit in patients with Alzheimer disease. Carome directs the Public Citizen Health Research Group, a nonprofit consumer advocacy organization that called the FDA's approval of aducanumab the "outrage of the month" for June.

"The FDA's decision showed a stunning disregard for science and eviscerated the agency's standards for approving new drugs," Carome wrote July 1 on his organization's website.

Jennifer Manly, PhD, a professor of neuropsychology in neurology at the Gertrude H. Sergievsky Center and the Taub Institute for Research on Aging and Alzheimer Disease and the Aging Brain at Columbia University, calls the focus on amyloid deposition "a fundamental disservice to the public."

"What we've done is created some compounds that are amazing at curing people of amyloidosis" but fail to slow cognitive decline, Manly told *JAMA*.

The FDA's approval of aducanumab was preordained, she said, pointing to a 2018 National Institute on Aging and Alzheimer Association "research framework" that defined Alzheimer disease not by its symptoms but "by its underlying pathologic processes that can be documented by postmortem examination or in vivo by biomarkers," such as amyloid-β deposition.

"Who was at the table when the table was set for this?" Manly asked, noting that the framework's multiple coauthors included Billy Dunn, MD, director of CDER's Office of New Drugs at the FDA, and Samantha Budd Haeberlein, PhD, senior vice president and head of the Neurodegeneration Development Unit at Biogen.

In December 2020, Carome called for an Office of Inspector General investigation and Dunn's temporary removal from his FDA position because of the agency's "inappropriate close collaboration with Biogen" before and after the company applied for approval of aducanumab. Instead of preparing separate briefing documents about aducanumab for the advisory committee, the FDA, supervised by Dunn, took the unprecedented step of preparing a joint briefing document with Biogen, Carome noted.

Woodcock responded to Carome via a letter in February. "FDA's interactions with sponsors are essential to set clear goals and expectations," she wrote. "In an increasingly scientifically complex landscape, the absence of these interactions would dramatically delay the availability of effective drugs for patients who need them."

In her July 9 letter to HHS Acting Inspector General Christi Grimm, MPA, asking for an independent review of aducanumab's approval process, Woodcock noted, "I have tremendous confidence in the integrity of the staff and leadership of [CDER] involved in the aducanumab review and their commitment to unbiased and science-based decision-making."

Define "Benefit"

Two identically designed and nearly simultaneous phase 3 trials assessed whether aducanumab not only reduced amyloid plaque but also met the primary end point of reducing patients' clinical decline, as measured by their scores on a test called the Clinical Dementia Rating–Sum of Boxes (CDR-SB) after 18 months.

The trials were both stopped early, before approximately half the participants completed them, because an independent data monitoring committee advised that aducanumab was unlikely to meet the primary end point.

Biogen then conducted a post hoc analysis that included additional follow-up data and concluded that one trial yielded positive results, the other null. However, Biogen said, subsets of participants in both trials who received higher doses of aducanumab demonstrated benefits. The company presented its findings in December 2019 at the Clinical Trials on Alzheimer Disease conference in San Diego, but the results have not been published in a peer-reviewed journal.

However, Biogen presented no convincing evidence that correlated biomarker changes to cognitive benefits, noted a perspective article published online last November and coauthored by Mayo Clinic neurologist David Knopman, MD, 1 of the 3 members who resigned from the advisory committee after the FDA approved aducanumab. Knopman was recused from the meeting at which the drug was reviewed because he served as a site investigator for 1 of its phase 3 trials.

Knopman and his coauthors, as others had, proposed that Biogen conduct a definitive third phase 3 trial optimally designed and adequately powered to prove efficacy before aducanumab was approved. "In a disease with high person-to-person heterogeneity in progression, obtaining [2] positive studies is more convincing than just one," Knopman's team wrote, noting that disease progression varied between the 2 phase 3 trial placebo groups. Still, "there is no consensus on what constitutes a clinically meaningful signal of benefit in [Alzheimer disease] therapeutics," the authors pointed out.

Stephen Salloway, MD, director of neurology and the Memory and Aging Program at Butler Hospital and professor of neurology and psychiatry at Brown University's Warren Alpert Medical School, has been a site principal investigator for phase 1 and phase 3 trials of aducanumab, cochaired the investigative steering committee for phase 3 trials, and advised Biogen on safety protocols and adverse effect management. The first aducanumab infusion given outside a clinical trial was administered June 16 at Butler Hospital.

"I understand the critics, and I love them. They're my friends and my colleagues," Salloway said in an interview.

"I don't happen to agree with their interpretation of the same data set."

Of 17 patients he's observed receiving long-term aducanumab therapy—first in the phase 1 trial and then in the open-label extension—10 have been more stable than expected, Salloway said, adding that he doesn't have data about whether the more stable patients had better amyloid clearance than those whose disease advanced more.

"Progress is often controversial," he said. "The data have issues, no doubt about it."

Might Timing Be Everything?

One possible reason that antiamyloid therapies have failed to show a clinical benefit is that they might have been given too late in the course of Alzheimer disease, said Todd Golde, MD, PhD, director of the Evelyn F. and William L. McKnight Brain Institute and the Florida Alzheimer's Disease Research Center at the University of Florida College of Medicine.

"If amyloid is the trigger of the disease, and you're trying to treat the trigger at a stage where the disease is independent of it," the therapy is bound to fail, Golde, who describes himself as "an amyloid guy," told *JAMA*. At that point, Golde said, treating Alzheimer disease with an antiamyloid therapy is like starting patients with statins after they've had 4 myocardial infarctions and are in heart failure.

Salloway called aducanumab's approval "a turning point in the treatment of Alzheimer's," because "it urges us to diagnose earlier…and to make a more definitive diagnosis."

Golde and Salloway advocate conducting prevention trials in people whose brains are accumulating amyloid plaque but still have normal cognition. Salloway is an investigator with one such study, which is comparing Biogen and Eisai's lecanemab, another antiamyloid monoclonal antibody, vs a placebo in cognitively normal people as young as 55 years who have PET-confirmed amyloid plaque.

As for aducanumab, though, "there is no evidence that this medicine will prevent Alzheimer's disease, and it would be irresponsible to prescribe it to [asymptomatic] people without evidence, given that the safety profile is not benign," Levey said.

Even without treatment, many people in the lecanemab trial might never develop symptoms of Alzheimer disease. Autopsy studies suggest that 30% to 40% of people in their 70s have amyloid deposits in their brain but normal cognition, Schneider noted.

Narrowing It Down

Although aducanumab was tested only in people with mild cognitive impairment, which can progress to Alzheimer disease, or mild dementia due to Alzheimer disease, the FDA initially approved it for anyone with Alzheimer disease. In the US, that's 6.2 million people, according to the FDA. "With the broad label it really could be the wild, wild west," Levey said at the time. He and other dementia specialists expressed hope that payors such as Medicare would step in and limit coverage only to the types of patients in the clinical trials.

A month after the FDA approved aducanumab, though, the agency changed the indications section on the drug's label. Instead of anyone with Alzheimer disease, treatment should be initiated only in patients with mild cognitive impairment (MCI) due to Alzheimer disease or mild Alzheimer disease—the populations studied in the clinical trials.

"In my view, there is still room for improvement, but this definitely is an important revision to the label," Levey told *JAMA*.

Salloway called the updated label "welcome news." The narrower indication "will benefit both patients and providers," he said.

Recognizing the need for clarification about who should start aducanumab therapy, Salloway said, he and a small group of fellow dementia specialists began work on a guidance for clinicians as soon as the drug was approved. In mid-July, he said the document would soon be published.

After the FDA approved aducanumab, the American Academy of Neurology (AAN) posted a document entitled "How to Talk to Your Patients About Aducanumab."

The AAN notes that, according to the drug's label, patients require brain magnetic resonance imaging (MRI) within a year before their first infusion and additional brain MRIs before their 7th and 12th infusions. The scans are needed to monitor for amyloid-related imaging abnormalities (ARIAs). As the AAN document notes, 35% of clinical trial participants who received aducanumab (compared with 3% of those who received a placebo) developed ARIAs, with either swelling or bleeding in the brain, within the first 4 months of treatment with aducanumab. ARIA symptoms include confusion, altered mental status, and disorientation.

ARIAs usually resolved over time, but at least 1 clinical trial participant required hospitalization in an intensive care unit before his symptoms—soaring blood pressure, explosive headaches, and the inability to read—resolved.

A case report noted that the patient carried 2 copies of the *APOE*ε4* allele, which is not only the most common genetic risk factor for Alzheimer disease but has also been linked to a greater risk of ARIAs. "Risk stratification with APOE ε4 genotyping may help guide treatment decisions," the case report authors wrote, although the aducanumab label doesn't mention a need to determine patients' *APOE* status before starting treatment.

Perhaps even more surprising, the aducanumab label doesn't advise prescribers to confirm that treatment candidates do indeed have amyloid deposition in their brains. "Probably 20% to 30% of people who get a diagnosis of Alzheimer disease in the real world don't have it," Levey said.

Down the Road

The FDA's approval of aducanumab could have far-reaching implications for Alzheimer disease treatments.

In a prepared statement headlined "It's a New Day in the Fight Against Alzheimer's," the Alzheimer's Association called aducanumab's approval "a milestone in the treatment of the disease and a beginning of a completely new future for Alzheimer's treatments."

Whether that future will be bright remains to be seen.

"After the FDA approved 1 drug based on a surrogate measure, that set precedent for future reviews," noted Aaron Kesselheim, MD, JD, MPH, director of the Program on Regulation, Therapeutics, and Law at Harvard Medical School and the Brigham and Women's Hospital, who resigned from the FDA advisory committee after aducanumab's approval. "It's hard for the FDA to then be selective afterward."

Indeed, 2 weeks after approving aducanumab, the FDA designated 2 other antiamyloid monoclonal antibodies as fast-track "breakthrough therapies." One was lecanemab; the other was Lilly's donanemab. They target different points in the amyloid cascade than aducanumab.

The breakthrough therapy designation is "designed to expedite the development and review of drugs that are intended to treat a serious condition," according to the FDA. Such drugs meet a "clinically significant endpoint," which, the FDA says, can be an effect on "an established surrogate endpoint," such as amyloid plaque.

A phase 2 trial, published in May, found that compared with placebo, donanemab resulted in 25% to 30% less decline in scores on the Integrated Alzheimer Disease Rating Scale, which measures cognition and the ability to perform activities of daily living. However, Levey wrote in an accompanying editorial, the findings, which amounted to a 3-point difference on a scale of 0 to 144, "barely showed significance."

The donanemab trial results were encouraging, but "the need for additional research has never been clearer," Levey wrote. "Much remains to be discovered about how to translate research into clinical practice with treatments for Alzheimer's disease that are widely available."

Now that aducanumab is on the market, it could become more difficult to enroll and keep patients in placebo-controlled trials of investigational Alzheimer disease therapies.

"We are concerned," said Jason Karlawish, MD, codirector of the Penn Memory Center, where he oversees the Anti-Amyloid Treatment in Asymptomatic Alzheimer (A4) study, which is testing solanezumab, a Lilly antiamyloid monoclonal antibody, in people who at baseline had amyloid-positive PET scans but passed a battery of cognitive tests.

However, Salloway said, concern about the feasibility of placebo-controlled trials of other therapies "is not a reason not to approve a medicine." If aducanumab were to become the standard of care for treating people with mild cognitive impairment and early Alzheimer disease, US trials of other potential therapies would have to provide it to participants, he said.

But what if aducanumab was the drug being studied, as in its required phase 4 trial? "I think it will be very difficult for Biogen to conduct a randomized, placebo-controlled trial of the drug in the US," Karlawish said.

In its approval letter to Biogen, the FDA said the postmarket trial must be completed by August 2029 with the final report of its findings due in February 2030—more than 8½ years after approval. In a June 23 statement, Biogen and Eisai said they were "working with urgency" toward completing the confirmatory trial ahead of the 2029 deadline.

To Prescribe, or Not to Prescribe?

A week before the FDA approved aducanumab, Karlawish published an opinion piece saying he wouldn't prescribe the drug if the agency greenlighted it because "Biogen hasn't made a convincing case for it."

Now that aducanumab has been approved, he's changed his stance somewhat. "I will describe myself as a reluctant prescriber," Karlawish told *JAMA*.

Although he isn't convinced the drug will benefit patients, Karlawish said, he feels it is important to respect patient autonomy. "After discussion of the complexities of this drug, risks, and benefits, if someone wants to take it, I will prescribe it."

Golde, who focuses on research and no longer sees patients in the clinic, said he doesn't expect aducanumab to be widely prescribed. "I can tell you in general that there is not a lot of enthusiasm from my colleagues," he said. "In the best case, they certainly won't encourage people to try to take it. In most cases they'll try to discourage them."

In mid-July, 2 large health systems said that for now, at least, if their physicians prescribe the drug, patients will have to go elsewhere to get it.

After reviewing all available scientific data about aducanumab, "Cleveland Clinic will not be carrying the drug on our formulary," although it will reevaluate the medication when additional data become available, a spokeswoman told *JAMA*.

New York's Mount Sinai Health System won't decide whether to administer aducanumab until 3 steps are completed, Sam Gandy, MD, PhD, director of the Mount Sinai Center for Cognitive Health, told *JAMA*. Mount Sinai must finish its medication best practices assessment and review of all scientific data about aducanumab, Gandy said, and the HHS inspector general's office must finish its investigation of the FDA-Biogen relationship.

Although he's not going to recommend that patients take aducanumab, Schneider said that if they bring it up, "I'm going to inform them. I'm not going to stand in their way if they wish to take it. I may or may not write the final script, but there are plenty of other physicians here who would." ■

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