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FDA Gives Accelerated Approval for Risky Alzheimer's Pill

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STORY AT-A-GLANCE

- The U.S. Food and Drug Administration (FDA) granted accelerated approval for the Alzheimer's disease drug lecanemab (Leqembi)
- The drug, a monoclonal antibody, binds to amyloid beta in the brain
- The most common reactions included amyloid-related imaging abnormalities, or ARIA, which involves swelling and bleeding in the brain that can be life-threatening. During the trial, ARIA occurred more often in people with the APOE4 gene, which is considered to be the strongest risk factor for Alzheimer's disease
- Amyloid beta may be a symptom of Alzheimer's — not the cause — and could even have a protective role in the disease process
- This means drugs that work by reducing amyloid beta may be missing the problem entirely, putting patients at risk of serious adverse events for little to no benefit

The U.S. Food and Drug Administration granted accelerated approval for the Alzheimer's disease drug lecanemab (Leqembi). The drug, a monoclonal antibody, binds to amyloid beta in the brain.

An 18-month study published in the New England Journal of Medicine[1] found Leqembi reduced markers of amyloid in early Alzheimer's disease and led to "moderately less decline" in cognition and function compared to placebo. However, the study added, the drug was "associated with adverse events."[2]

The FDA granted accelerated approval of Leqembi based on the observed reduction of amyloid beta plaque. The study involved 856 patients with Alzheimer's disease, with drug treatment started at the point of mild cognitive impairment or mild dementia, along with the confirmed presence of amyloid beta. According to the FDA:[3]

> *"Patients receiving the treatment had significant dose- and time-dependent reduction of amyloid beta plaque, with patients receiving the approved dose of lecanemab, 10 milligram/kilogram every two weeks, having a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm, which had no reduction of amyloid beta plaque."*

Alzheimer's Drug Linked to Life-Threatening Brain Bleeding

Serious adverse events were reported in 14% of those taking the drug, and 6.9% of subjects in the Leqembi group dropped out of the trial due to the adverse events.[4] Along with reactions to the intravenous infusion — Leqembi is given intravenously — the most common reactions included amyloid-related imaging abnormalities, or ARIA, which can be life-threatening.[5]

ARIA may manifest as brain edema, or swelling (ARIA-E), or bleeding in the brain, known as ARIA-H, for hemorrhage.[6] Brain bleeding occurred in 17.3% of those taking Leqembi, compared to 9% of those in the placebo group. Brain swelling occurred in 12.6% of those in the Leqembi group, compared to 1.7% of the placebo group.[7] ARIA occurred more often in people with the APOE4 gene, which is considered to be the strongest risk factor for Alzheimer's disease.[8]

Dr. Richard Isaacson, director of the Alzheimer's Prevention Clinic in the Center for Brain Health at Florida Atlantic University's Schmidt College of Medicine, told CNN:[9]

> *"I will prescribe this drug in the right person, at the right dose and in a very carefully monitored way, but this drug is not for everyone ... I would do genetic testing for APOE4 first. I would have a frank discussion with my patients.*

If someone is having side effects, if someone is on a blood-thinning medication, if someone has a problem, they need to discuss this with the treating physician, and they need to seek medical attention immediately."

Leqembi's wholesale price has been set at $26,500 per patient per year. This dropped from the $56,000 it was initially slated to cost, due to insurance companies threatening not to cover it.[10] The prescribing information for Leqembi includes a warning for ARIA, which usually occurs without symptoms, though it can lead to life-threatening events. In a news release about the drug's accelerated approval, the FDA noted:[11]

"ARIA most commonly presents as temporary swelling in areas of the brain that usually resolves over time and may be accompanied by small spots of bleeding in or on the surface of the brain, though some people may have symptoms such as headache, confusion, dizziness, vision changes, nausea and seizure.

Another warning for Leqembi is for a risk of infusion-related reactions, with symptoms such as flu-like symptoms, nausea, vomiting and changes in blood pressure. The most common side effects of Leqembi were infusion-related reactions, headache and ARIA."

Alzheimer's Drug Aduhelm Also Raises Risk for ARIA

Aducanumab (brand name Aduhelm) is a monoclonal antibody similar to Leqembi. ARIA-E occurs in about one-third of people taking Aduhelm.[12] Similar to Leqembi, Aduhelm was brought to market under an accelerated approval pathway by the FDA, despite uncertainty about its clinical benefit.[13] Aduhelm's accelerated approval was so controversial that three members of the FDA's advisory panel resigned in protest.[14]

As an amyloid beta-directed antibody drug, Aduhelm also works by targeting amyloid beta in the brains of people with Alzheimer's disease, but the findings of ARIA-E in many taking the drugs are alarming.

Adam Brickman with Columbia University, New York City, suggested that the drug could potentially make cognitive decline worse instead of better. "It's hard to put a positive

spin on the neuroimaging abnormalities," he wrote. "... [W]e simply do not know the long-term consequences."[15]

While Aduhelm was approved in June 2021, an 18-month investigation revealed it involved "atypical collaboration" between the FDA and Biogen, the drug's maker, that was "rife with irregularities."[16] Biogen discontinued clinical trials for the drug in March 2019 after results suggested it wouldn't slow declines in memory, language and judgment in people with Alzheimer's.

However, the FDA then started a "working group" with Biogen to rekindle the drug, which involved extensive meetings and calls to guide the drug's approval. The collaboration was "unusual," to say the least. CNN reported:[17]

> *"The agency then collaborated with Biogen to draft a document used to brief an independent advisory committee that met in November 2020. The trial results were mixed, with only one showing a small benefit to patients.*
>
> *At that meeting, none of the committee's members voted to say that the studies presented strong evidence that the drug was effective at treating Alzheimer's. The meeting was unusual, according to one former FDA adviser who had sat on the committee for several years. Dr. Aaron Kesselheim told CNN in 2021 that the relationship between the FDA and the company was out of the ordinary."*

Kesselheim, who was one of the FDA advisory panel members who resigned to protest the drug's approval, called it "probably the worst drug approval decision in recent US history."[18]

FDA Also Fast-Tracked Alzheimer's Vaccine to Market

In what now appears to be an ongoing trend, the FDA also granted fast-track designation to UB-311, a vaccine for Alzheimer's disease made by biotechnology company Vaxxinity.[19] The shot is an anti-amyloid beta immunotherapeutic vaccine that, like Aduhelm and Leqembi, treats Alzheimer's disease by targeting aggregated amyloid beta in the brain.[20]

Phase 1, Phase 2a and Phase 2a Long-Term Extension trials have already been completed, with the company stating that the vaccine was "well tolerated in mild-to-moderate AD patients over three years of repeat dosing, with a safety profile comparable to placebo and no cases of amyloid-related imaging abnormalities-edema ("ARIA-E") in the main study."[21]

Vaxxinity has planned a Phase 2b trial,[22] but no one knows what the long-term consequences of this shot will be. To date, drug development for Alzheimer's has involved at least 300 failed trials.[23]

One study, which was a collaboration between Washington University in St. Louis, drug companies Eli Lilly and Roche, the National Institutes of Health and others, involved 194 participants, of which 52 took Roche's drug gantenerumab and 52 took Eli Lilly's solanezumab.[24]

The drugs were intended to remove amyloid beta (Aβ) from the brain, but they failed to achieve the primary outcome of the study, which was slowed cognitive decline, as measured by tests on thinking and memory. While the drugs did target amyloid beta, it had no effect on cognitive measures, with the researchers writing, "Both drugs engaged their Aβ targets but neither demonstrated a beneficial effect on cognitive measures compared to controls."[25]

Is Targeting Amyloid Beta Wise?

Amyloid beta may be a symptom of Alzheimer's — not the cause — and could even have a protective role in the disease process.[26] This means drugs and vaccines that work by reducing amyloid beta may be missing the problem entirely. Researchers from the Tokyo Metropolitan Institute of Medical Science, department of dementia and higher brain function, wrote in Frontiers in Neuroscience:[27]

> *"The so-called amyloid hypothesis, that the accumulation and deposition of oligomeric or fibrillar amyloid β (Aβ) peptide is the primary cause of Alzheimer's disease (AD), has been the mainstream concept underlying AD research for*

over 20 years. However, all attempts to develop Aβ-targeting drugs to treat AD have ended in failure."

In 2009, researchers brought attention to the misguided premise of oversimplifying Alzheimer's disease down to the amyloid-β protein precursor (AβPP) molecule, "implying that this molecule encapsulates AD so completely that the disease itself is almost of secondary importance." This, they noted, ignores "the complexity of chronic diseases in general" and added:[28]

"A great deal of attention has focused on amyloid-β as the major pathogenic mechanisms with the ultimate goal of using amyloid-β lowering therapies as an avenue of treatment.

Unfortunately, nearly a quarter century later, no tangible progress has been offered, whereas spectacular failure tends to be the most compelling. We have long contended, as has substantial literature, that proteinaceous accumulations are simply downstream and, often, endstage manifestations of disease.

Their overall poor correlation with the level of dementia, and their presence in the cognitively intact is evidence that is often ignored as an inconvenient truth. Current research examining amyloid oligomers, therefore, will add copious details to what is, in essence, a reductionist distraction from upstream pleiotrophic processes such as oxidative stress, cell cycle dysfunction, and inflammation.

It is now long overdue that the neuroscientists avoid the pitfall of perseverating on 'proteinopathies' and recognize that the continued targeting of end stage lesions in the face of repeated failure, or worse, is a losing proposition."

Are They Looking at Amyloid Beta All Wrong?

The brains of most elderly people contain amyloid beta, often in amounts similar to those found in patients with Alzheimer's disease.[29] It doesn't always lead to disease. Writing in the Annals of the New York Academy of Sciences, researchers suggested that

amyloid beta is a response to neuronal stress, one that functions as a protective adaptation to the disease.[30]

Amyloid beta, they argued, accumulates relatively late in the development of Alzheimer's disease, and while it has been found to be toxic in cell culture models, this may not hold true in humans. Instead of the prevailing notion that a mutation leads to increased amyloid beta, which leads to Alzheimer's, the team suggested that a mutation leads to Alzheimer's, which in turn triggers increased amyloid beta:[31]

> *"Mutations lead to cellular stress, which, in turn, leads to increased amyloid-β ... in AD, cellular stress precedes increases in amyloid-β ... Proteins, such as amyloid-β, that are induced under oxidative conditions and act to lessen oxidative damage are typically thought of as antioxidants and, in this regard, we recently demonstrated that amyloid-β is a bona fide antioxidant that can act as a potent superoxide dismutase."*

Researchers writing in Alzheimer's & Dementia, the Journal of the Alzheimer's Association, also suggest the accumulation of amyloid beta is a protective mechanism linked with glucose metabolism — albeit a protective mechanism that ultimately fails. They explained:[32]

> *"We predict that more Aβ accumulates in regions with higher rates of glucose metabolism, reaching a maximum followed by progression of pathology ... Aβ accumulation is characteristic of Alzheimer's disease (AD) but the accumulation does not correlate with cognitive decline, unlike the rates of glucose metabolism.*
>
> *... The claim explains the cognitive decline in some patients at a significantly lower level of Aβ deposition than in other patients, as well as the presence of cognitively healthy individuals with high Aβ accumulation. With further support of the hypothesis, the significance of Aβ accumulation in brains of patients with AD may require revision."*

Therefore, reliance on drugs to reduce amyloid beta may be, at best, misguided and, at worst, exposing patients to potentially life-threatening adverse effects for no benefit. Alzheimer's disease is a complex disease that requires a holistic approach for prevention and treatment.

One of the most comprehensive assessments of Alzheimer's risk is Dr. Dale Bredesen's ReCODE protocol, which evaluates 150 factors, including biochemistry, genetics and historical imaging, known to contribute to Alzheimer's disease.

In his book, "The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline,"[33] which describes the complete protocol, you will also find a list of suggested screening tests and the recommended ranges for each test, along with some of Bredesen's treatment suggestions, which include the use of exercise, ketogenic diet, optimizing vitamin D and other hormones, increasing sleep, meditation, detoxification and eliminating gluten and processed food.

For more details, you can download Bredesen's full-text case paper online, which details the full program.[34]

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