# Aducanumab (Aduhelm) for Alzheimer's Disease – a forgettable drug

Aduhelm (generic name: aducanumab) is being marketed as a proposed treatment for patients with Alzheimer's disease; its approval has become one of the most controversial decisions ever made by the Food and Drug Administration. **In 2019, its manufacturer, Biogen, stopped its clinical trials of the drug on the grounds of futility:** interim analysis of the data by its independent Data Safety Monitoring Board showed that the drug's performance was so poor that it was extremely unlikely it could be demonstrated to have any benefit.

Aduhelm had been designed to reduce the levels of visible amyloid protein deposits in the brain. This approach was based on the unproven hypothesis that because amyloid levels are higher in many (but by no means all) patients who died with Alzheimer's disease, lowering its levels might possibly improve clinical function in those patients. However, over the last two decades the so-called "amyloid hypothesis" has not translated into a successful target for therapeutics, as **many drugs that reduce production, inhibit aggregation, promote disaggregation, and increase brain clearance of beta-amyloid have not shown any clear effect on cognitive function.** There may be several reasons for this:

- Many patients with Alzheimer's disease do not have markedly elevated amyloid levels;

- At autopsy, many older patients who had good cognitive function have been found to have markedly elevated brain amyloid levels.

- "Amyloid" is not a single compound: this is a summary term describing many forms of protein, each of which has important subtypes. It isn't known which subtypes (if any) of amyloid are related to the causation of Alzheimer's disease, and which are not;

- Even if brain amyloid levels are elevated in a patient with Alzheimer's disease, it is not clear whether they are its cause, or simply formed in the course of the illness (or even in the course of aging itself), in which case reducing amyloid levels might have no effect on improving cognitive function.

- Measuring any of the many varieties of brain amyloid requires positron emission tomography (PET) scanning, a costly study that is not universally available.

After the failure of its clinical trial trials of Aduhelm in 2019, Biogen observed that even though the result was negative across the two trials, in the high-dose arm of one of the trials, patients' cognitive function diminished on average slightly less than placebo. But **the degree of change seen was so slight that it likely would not have been noticed by**

**families, patients, and clinicians.** Further, **cognitive function in the patients in the other similar trial showed no difference from placebo.**

With these unconvincing findings in place, Biogen held meetings with FDA officials to see if a different analysis of the study data could restore it to commercial viability. Some of these meetings appear to have been off-the-books "back channel" communications; irregularities in the approval process are being investigated by the Inspector General of the Department of Health and Human Services.

Together, the company and a small number of FDA officials identified various ways of looking at data from the clinical trials to make the case that the favorable findings in the one trial were "correct" and why the other negative findings were not. In such trials, it is generally agreed that **one does not accept a positive finding from patients in one trial if another comes to the opposite conclusion.** It is also not commonly accepted practice to perform new analyses of already-collected data after clinical trials have been completed to identify a favorable result when all prior analyses had found that there was none.

The validity of these post-hoc analyses was brought before an FDA advisory committee of outside experts in June 2021, at which all the available trial data were presented and discussed in detail. These advisers represented medical school faculty and practitioners from all over the country who had particular expertise in these matters, including the fields of neurology, neuroscience, geriatrics, and internal medicine. FDA officials instructed committee members to base their decision on whether Aduhelm produced clinical benefit in treating cognitive impairment in study subjects, compared to study subjects given placebo. An FDA official explicitly noted that the drug's evaluation should be based on its effect on patients' cognition, and not on changes in amyloid levels in the brain. This was because amyloid levels were considered a second-best "surrogate measure" that might or might not be predictive of patient benefit.

While the clinical trials of Aduhelm were not convincing in demonstrating benefit, they did document a worrisome side effect. **In up to 40% of patients receiving the higher dose in these studies (the dose approved for clinical use), MRI scans showed that they had developed cerebral swelling;** in some of those patients this progressed to cerebral hemorrhage. This concerning condition was given the benign- and musical-sounding name of ARIA, for Amyloid-Related Imaging Abnormalities. A higher proportion of patients given the high dose also reported headaches. As a result of the cerebral swelling findings, the approval of Aduhelm would mean that in addition to the costly PET scans that would be necessary to identify patients who might be treated, those taking the drug would need to undergo periodic MRI scans to detect the occurrence of cerebral swelling.

The advisory committee considered the absence of convincing measures of clinical benefit, compared to the risk of potentially serious cerebral swelling and occasional hemorrhage. The formal presentation by FDA's own statisticians confirmed that when all the data were taken into account, the drug failed to demonstrate an advantage over placebo. **The committee concluded that taken as a whole, the complete set of clinical trial data did not produce convincing evidence that patients randomized to**

**aducanumab had better cognitive performance than those randomized to placebo.** The committee was also concerned about the widespread and potentially serious side effects. In light of these findings, the group overwhelmingly recommended that Aduhelm not be approved. The vote was 10 to 0, with one abstention. (The single advisor who abstained did so because he had been involved in earlier studies of the drug, and did not want to create the impression of a conflict of interest. Interviewed later, he said that if he had voted, he would have also voted against the drug.) However, FDA advisory committee decisions are not binding; the final approval decision for a drug rests in the hands of the FDA Commissioner. Commissioners generally respect the recommendation of advisory committees, especially when that determination is as lopsided as this one, but doing so is not legally required.

The failure of Biogen to produce compelling evidence of the drug's effectiveness was a disappointment to patients and families suffering with Alzheimer's disease. It is a crushing disability that effects tens of millions of Americans, and many more around the world. Two earlier drug classes have long been approved to treat the condition (the cholinesterase inhibitors and memantine), but they are widely seen as having minimal effects at best in most patients.

In the run-up to the final FDA decision on Aduhelm, Biogen launched or helped fund multiple campaigns to promote use of the drug. Although a company cannot advertise a product that has not been FDA-approved, Biogen created and widely promoted a website to "sensitize" potential patients and their caregivers about Alzheimer's disease. It presented examples of common cognitive lapses, such as not being able to recall where one put something, or difficulty finding a particular word, and noted that they were possible signs of the onset of Alzheimer's disease. One medical school faculty member had young members of her research staff take this "test," with the result that many were told to see their doctors about a possible diagnosis of dementia, and to talk about potential treatments for it. Another Biogen website aimed at health care professionals identified clinicians and diagnostic imaging centers to help conduct their workup and eventual treatment. The company also contributed financially to a group identifying itself as representing patient needs, the Alzheimer's Association, which became an aggressive advocate for approval of the drug. Concern grew that when the drug was approved, clinicians might be persuaded to use it because of their understandable desire to do anything possible for their patients, encouraged by desperate family members. Incentives to use the drug would also be built into the fees available to physicians for administering the monthly infusions, as well as the mark-up on a very expensive doctor-provided treatment. Some observers saw the drug as a potential financial windfall for Alzheimer's disease clinics and "memory centers" caring for such patients.

In light of the poor evidence on Aduhelm and the solidly negative recommendation of the FDA advisory committee, most observers were surprised when Acting FDA Commissioner Janet Woodcock announced in June 2021 that the FDA was approving Aduhelm for use in patients with Alzheimer's disease. Although the drug had been studied only in patients with mild Alzheimer's disease, the original FDA-approved indication authorized its use for patients with all stages of Alzheimer's disease, including those with

moderate to severe forms of the condition, who had not been studied in Biogen's clinical trials.

The FDA's justified the approval decision in a novel way: after the normal evaluation process had been completed, **the agency changed its assessment method from the normal evaluation pathway to its Accelerated Approval pathway, which allows a decision on a drug to be based on changes in laboratory tests or other measures, rather than clinical findings.** The official FDA statement noted that the drug was approved not on the basis of improvement in the symptoms of Alzheimer's disease in trial patients (since this had not been convincingly demonstrated), but instead on the basis of the lowering of brain amyloid levels, despite the controversial nature of the relationship between this finding and clinical benefit – a discrepancy that had been noted by the FDA's own statisticians. FDA's Accelerated Approval program, which has been the subject of considerable controversy, allows for acceptance of a new drug based only on its effect on a "surrogate measure" such as an imaging study (as was the case here), or a laboratory test result, or other such measures, rather than a clinical endpoint (how a patient feels, functions or survives). All that is required for an affirmative Accelerated Approval decision is that the surrogate measure be "reasonably expected" to predict a clinical change. However, the regulation does not specify criteria for what is "reasonable" in this setting, and who is doing the expecting. This after-the-fact change in evaluation criteria was seen as especially problematic since many neuroscientists and neurologists did not agree that the changes in amyloid levels seen in the Aduhelm study would "reasonably be expected" to predict patient benefit.

The accelerated approval program requires that drugs approved on the basis of such second-best tests be subject to a follow-up confirmatory clinical trial to show that the new medication can provide some clinical benefit. However, in the case of Aduhelm, **FDA gave the company a full nine years to complete such studies, a remarkably long time for a condition as prevalent as Alzheimer's disease,** raising questions about the relation between the decision and the spirit of the regulations concerning such approvals.

Aduhelm must be given via intravenous infusion every month, in a physician's office or infusion center. **Because of the high risk of cerebral swelling, patients must be followed up regularly with additional MRI scans** to detect these changes and enable the physician to lower the dose to try to prevent these changes from progressing to more serious damage.

Once the drug was approved, Biogen announced a price that translated to an annual cost of $56,000 for an average patient just for the medication; this would not include the costs of the medical care required for the monthly infusion treatments, or the regular MRI scans needed for to detect brain swelling or hemorrhage. Policy analysts calculated that at this initial price, and given the very broad indications that FDA had initially permitted, use of the drug among the nation's millions of Alzheimer's patients could amount to $6-29 billion each year; the upper estimate would exceed the annual budget for NASA.

Other scientists throughout the US and the world did independent evaluations of the data on Aduhelm, and came to very different conclusions. Within weeks of the FDA decision, **a number of the nation's most prominent health care systems announced that they would not be offering their patients the drug because it simply had not shown adequate efficacy in the face of its meaningful risks.** These included the Cleveland Clinic, the Mount Sinai Medical Center in New York, the Mass General Brigham health care system in Boston, and several Blue Cross plans around the country. Several other insurers, among them non-profits, stated that they would not cover the drug on the grounds that scarce health care resources would be better spent on treatments that had been shown to be both safe and effective. **Drug regulators in Canada, Europe, and Japan refused to approve the drug for use.** Individual physicians, patients, and families also took notice: in the months that followed, uptake of the drug was minuscule, with Biogen admitting months after approval that only a few hundred patients had actually been treated – far fewer than the windfall they had expected.

In the months after FDA's initial approval decision, several small attempts were made to course-correct. FDA limited the drug approval to patients with mild Alzheimer's disease, rather than those with moderate or severe symptoms in whom the drug had never been studied, and in whom the relevance of the idea of reducing amyloid levels seemed even less defensible. **A group of senior clinicians and scientists from around the country condemned the FDA approval decision and called on the agency to take the drug off the market, demanding its "accelerated withdrawal,"** to match the "accelerated approval" pathway the agency had used to approve the drug. At the same time as the scientists' statement of condemnation Biogen, which had been pilloried for setting a price amounting to $56,000 per year for a drug with such poor credentials, cut its price in half "to make the product more available to larger numbers of patients in need."

At the start of 2022, attention shifted to the federal Centers for Medicaid and Medicare services (CMS), which is responsible for the Medicare program. The Office of the Medicare Actuary, which is responsible for calculating the federal program's projected expenditures each year so that the premium charged to patients can be adjusted accordingly, had determined in December 2021 that **the expected addition of the cost of Aduhelm would contribute to the need to sharply raise the premium for all Medicare beneficiaries in its Part B program from $158 to $170 per month; half of that increase was attributed to the expected cost of covering Aduhelm.** Traditionally, Medicare pays for all FDA approved drugs, generally at whatever price the manufacturer demands. As a result, there was great interest in whether the federal program would continue this practice, which would have been an economic windfall for Biogen, even if it would not have produced much benefit for Medicare enrollees. It was therefore a striking when in January the Medicare program made an initial determination that it would not cover Aduhelm except for patients in authorized clinical trials, making it the first FDA approved medication for which Medicare refused to pay. A final decision on payment will be made in April. Given the billions of dollars of sales at stake, Biogen and its allies have been lobbying the government heavily to change that decision.

Where does this leave patients and health care professionals?

The CMS preliminary refusal to cover Aduhelm outside of clinical trials is a sensible one, since the drug has not convincingly demonstrated benefit but has convincingly demonstrated avoidable harm. Clinicians still have options in caring for their patients with cognitive impairment just as before. These include:

- **Conducting a thorough workup** to look for the uncommon but treatable causes of cognitive impairment, such as hypothyroidism, vitamin $B_{12}$ deficiency, and other chronic illnesses and potentially reversible conditions;
- **Referral of patients and families to information sources and resources** that emphasize non-drug ways of dealing with Alzheimer's disease.

Nonetheless, patients and families are likely to continue to ask about the drug and seek access to it, and some insurers may cover it. It is important for health care professionals (physicians, nurse practitioners, pharmacists, physician assistants, and social workers) to be able to communicate the facts about this medication accurately to patients and families, and to make it clear that they are not withholding a valuable treatment simply because of reimbursement concerns. To help accomplish that, Alosa has created materials that can be distributed to them, explaining the issues for a lay audience, available at www.AlosaHealth.org .

Hopefully, in the coming years, continuing research will discover a medication to help manage Alzheimer's disease, and perhaps even prevent its occurrence. But that is not the reality that clinicians, patients and families must live with now. Until that day, we are left with the same realities we have learned to live with in recent years: evaluation and treatment of possible contributing conditions, use of non-drug alternatives that can help lessen the crushing burden of this condition for patients and their caregivers, and – above all – compassion.

*Creation of this material was supported by a grant from the John A. Hartford Foundation.*