DAA DISCUSSION POINTS ABOUT CMS' DRAFT DECISION ON ANTI-AMYLOID MONOCLONAL ANTIBODY DRUGS, INCLUDING ADUCANUMAB (aka Aduhelm™)

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On January 11, 2022 CMS announced it would cover FDA-approved anti-amyloid monoclonal antibody drugs for people with Alzheimer's on Medicare only if they were enrolled in a qualifying clinical trial. This is a controversial decision and CMS would like to hear what people living with dementia, their families and other stakeholders think about it.

What is aducanumab?

Aducanumab is an anti-amyloid monoclonal antibody drug that targets amyloid beta. It's a way of getting the body's immune system to get rid of the amyloid. Why target amyloid beta? Amyloid beta plays a role in the development and progression of Alzheimer's Disease. Since the early 2000's, over 20 drugs have targeted amyloid;not one has produced benefit; some have had serious risks. Six are the monoclonal antibody type; more are in Phase 3 trials.

How do drugs get approved in the U.S.?

When a drug manufacturer wants to develop a new drug, it goes through a process. In the United States, a drug developer submits an application to the FDA (Food and Drug Administration) describing what the drug is, how it is made, and what the plan is for testing in humans.

If the FDA agrees that risks have been addressed and human subjects are protected, the drug moves to clinical trials. There are 3 phases of clinical trials before a drug can move to approval. Each phase addresses different questions.

- In phase 1, how does it work in the human body? Is it safe? What are the side effects? Usually involves 30-40 healthy people.
- In phase 2, is it safe and does it work for the condition it was developed

(efficacy). Some kind of baseline test is used, the drug is given, and then the test is repeated. Usually 100-200 people with the condition are enrolled.

- In phase 3, further refinements of dosing, safety and efficacy (the "does it work" question). Before phase 3 begins, criteria are set that will stop the clinical trial early if there are serious adverse effects or if the drug shows "futility" meaning the drug doesn't seem to be working. 1000+ individuals are typically enrolled in Phase 3.

Aducanumab went through all of these steps. How did it become so controversial?

- In March, 2019 Biogen halted its Phase 3 clinical trials because the drug appeared futile.

- In October, 2019, Biogen reversed its decision saying it had reanalyzed the data and found that there was a small but statistically significant change in the test used to study whether or not it worked.

- A year later, in November 2020, an 11-member independent advisory group at the FDA reviewed all the data and recommended against approval (10-0 with one abstention). There were no votes for approval. Their reason: it was not clear that the drug had any benefit and it carried serious adverse effects, including headaches, dizziness, falls, brain bleeds and swelling.

- On March 31 and April 7, 2021, a 15-member council of senior FDA officials recommended against approval. The evidence did not meet the threshold for "instilling public confidence in the usefulness of the drug," according to the minutes. Another trial was necessary, the council agreed, but could be "a shorter and more efficient trial." During the public meeting, the council voted unanimously (15-0) that the evidence was not adequate to demonstrate that aducanumab plus supportive care provides a net health benefit when compared to supportive care alone.

- On June 7th, 2021, the FDA announced it would approve Aduhelm™ using an accelerated approval process that does not require the drug developer to show that the drug actually improves clinical outcomes. That is, the drug does not have to show that it actually benefits the patient, only that it could. Biogen only had to show that its drug affects some part of the disease process and agree to continue studies to show it works. Aducanumab does lower amyloid levels and it was approved on that

basis.

The Controversy

Biogen, the Alzheimer's Association and UsAgainst Alzheimer's praised the decision as historic, citing how long it had been since a new drug for Alzheimer's had been approved and that it was important given the unmet need for new treatments."Having one, finally one, even one (drug) that falls short of perfect, adds value." (Alzheimer's Association)

Others were more critical: The FDA had approved the drug even though a council of its own senior officials, an external independent advisory group of outside experts, and many Alzheimer's specialists said it was unclear that the drug had benefits and that it carried serious risks.

As a result of the FDA's accelerated approval for aducanumab -

- 3 physician members of the advisory group resigned in protest.
- Major hospital systems refused to prescribe or administer the drug.
- Many private insurers declined to pay for the drug.

Biogen set a price of $56,000/year for the drug.

An independent body, the Institute for Clinical and Economic Review's (ICER), also analyzed the study results, talked with patient groups and clinical experts, and worked with the manufacturer to understand their position. ICER concluded the current evidence was insufficient to show that aducanumab slows cognitive decline but was clear that it can harm some patients. ICER's cost-effectiveness analysis said the drug should be priced between about $3,000 per year and $8,400, which is far less than Biogen's price of $56,000.

ICER made these recommendations -

- Reduce the price to avoid strain on Medicare and Medicaid budgets and to avert financial toxicity for patients.
- Urge experts and policymakers not to overstate the potential benefits.
- Explore options for insurance coverage criteria.
- Suggest specific rigorous research designs as part of any potential Medicare coverage decision.

Other experts warned that given the size of the patient population, aducanumab could

have significant cost implications for Medicare and its beneficiaries. Kaiser Family Foundation stated - "If just one-quarter of eligible beneficiaries are prescribed aducanumab, the total spending for it in one year alone would be nearly $29 billion. To put this $29 billion amount in context, total Medicare spending for all Part B drugs was $37 billion in 2019.

CMS reviewed the impact on Medicare spending and raised premiums in Fall 2021 saying a significant portion of the 14.5% needed increase for 2022 Part B premiums was due to aducanumab's approval. The price of aducanumab does not include the cost of the infusion or the necessary monitoring with brain scans.

In December 2021, Biogen cut the price to $28,000/year.

What happens next?

CMS uses a national coverage determination to evaluate whether a drug meets its standard of **reasonable and necessary**. This standard is different from the FDA's safe and effective standard. The national coverage determination process can have several outcomes:

- CMS would not cover the drug at all;
- CMS would cover the drug without question;
- CMS would cover the drug with limitations on how long it can be prescribed;
- CMS would cover the drug with evidence development limitations.

CMS opted for the last option as a temporary decision - It would only cover anti-amyloid monoclonal antibody drugs, including aducanumab, for people enrolled in CMS-approved or NIH-supported randomized clinical trials.

Perhaps the most controversial aspect of the draft decision was how broad a brush it applied. Rather than placing a limitation on aducanumab, CMS placed a limitation on all anti-amyloid monoclonal antibody drugs. There are a number of others currently in clinical trials. Gantenerumab (Roche) and lecanemab (Eisai) are expected to have Phase 3 clinical trial data this year and donanemab (Eli Lilly) soon after. Many Alzheimer's researchers feel that each anti-amyloid monoclonal antibody drug should be assessed on its own merits after successfully completing Phase 3 trials.

Summary

Points in support of CMS' decision -

- There is scant evidence this drug works. Approving coverage with evidence development limitation represents a reasonable compromise between access to a new drug and patient safety.
- FDA's accelerated approval process gave CMS a drug with questionable value; CMS' decision corrects that. "FDA made a mistake with its accelerated approval," Karlawish said. "Most of the field has arrived at the conclusion. So in a sense, CMS is redressing that." (The Washington Post)
- Daniel Gibbs, a retired neurologist at Oregon Health and Science University, Portland, participated in the ENGAGE Phase 3 trial of aducanumab and survived severe ARIA that required hospitalization. "Those potentially life-threatening side effects should not be taken lightly. The CMS decision offers a reasonable path forward," he wrote. (AlzForum)
- Aducanumab treatment can cause the brain bleeds and edema known as ARIA (Amyloid-Related Imaging Abnormalities). Many clinicians fear this would be less well managed in general healthcare practitioner practices than in clinical trials.
- Financial burden on patients and families would be enormous.
- The CMS mandate to increase diversity of participants is appropriate and necessary. Black Americans are disproportionately affected by Alzheimer's Disease and have been underrepresented in clinical trials. (AlzForum)

Points in opposition of CMS decision -

- "CMS's preliminary decision to delay and restrict coverage for the first disease modifying drug for Alzheimer's is unprecedented, reckless, and stands in direct opposition to the President's personal commitment to better address the Alzheimer's public health crisis in the U.S. and improve access to life prolonging Alzheimer's therapies for all Americans". (Global Alzheimer's Platform)
- Restricts access to people living with Alzheimer's by requiring enrollment in trials.
- Unfairly restricts new monoclonal antibody drugs in general.
- The CMS mandate to increase diversity of participants is impractical and unworkable even if desirable. The diversity bar is set too high, can't be achieved and may ultimately prove counterproductive (AlzForum).

Sources for this paper include -

<u>Articles</u> - New York Times, The Washington Post, Health Affairs Magazine, the Journal of the American Medical Association

<u>Websites</u> – AlzForum, Kaiser Family Foundation, Alzheimer's Association, Global Alzheimer's Platform, UsAgainstAlzheimer's, ICER, Biogen