The Aducanumab Controversy

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Contributor: Allison B. Reiss

Finding treatments and cures for Alzheimer's disease (AD) has been extremely challenging and progress has been slow with many disappointments. Progress achieved using animals in research has rarely been replicated in humans. An example of the animal-to-human disconnect is the poor performance of amyloid-clearing antibodies in human trials. On June 7, aducanumab, an anti-amyloid monoclonal antibody, was granted accelerated approval by the FDA despite lack of support from its own Advisory Committee. In my opinion as an Alzheimer's researcher and internal medicine physician, this ill-considered decision is a mistake that will cause major setbacks in AD drug discovery, will harm the AD community and will lead to distrust of future treatments that actually work. This article reflects the opinion of this author alone.

Alzheimer's disease   amyloid   antibody   aducanumab

1. Background

As a physician and scientist actively seeking an effective treatment for Alzheimer's disease (AD), I have been following the story of aducanumab closely. After reading the JAMA viewpoint piece in March, ([1]), I was fairly confident that the Food and Drug Administration (FDA) would not put this drug on the market. In fact, I expressed my skepticism about aducanumab on May 26 during a symposium held by the NYU Langone Health Center for Cognitive Neurology. Many of us working in the field, myself included, were stunned by the FDA's decision, especially in light of the fact that the agency overrode the advice given by its own advisory panel. In fact, three members of that panel, Joel S. Perlmutter, David S. Knopman, and Aaron Kesselheim have resigned in protest, and I applaud their integrity and courage in taking a stand.

2. Evidence to support view

Why am I opposed to the marketing of this antibody medication? In a nutshell, because it offers false hope, will erode trust and cause devastating adverse effects like brain swelling in some people. The risk-to-benefit ratio is highly unfavorable. I am both an internal medicine physician and a molecular biologist, so I try to see AD from a broad perspective. I have the privilege of meeting with and talking to many persons living with AD, their families and caregivers. Their pain is palpable yet they never lose hope. They inspire my research every day. Our current treatment options offer only modest relief of symptoms and there is an urgent need for a real breakthrough. Aducanumab is not that leap forward. It is one of a number of antibody treatments designed to clear amyloid from the brain under the assumption that amyloid accumulation is responsible for the pathogenesis of AD. In mice genetically engineered to accumulate amyloid in the brain, drugs of this class work very well, but, at the risk of

stating the obvious, people are not mice. As noted in a paper from my group published in *Journal of Investigative Medicine* last year ([2]), the failed human trials should teach us a simple, but important lesson about accepting results and moving on ([3]). It is my professional opinion that the idea that clearing amyloid will alleviate AD is fundamentally flawed - we need to go back to first principles and look at mechanism at the molecular level. That is what a lot of us are doing. The results of the trials on aducanumab have been interpreted in different ways, but it is my contention that the real-life effects on persons with AD will be imperceptible at a price of about $56,000 a year per patient. For more on the meager clinical benefits, I refer you to Kathy Y. Liu's paper just published in Lancet Psychiatry ([4]).

It is important that, no matter what happens with aducanumab, the AD community remains optimistic. Scientists worldwide are in their laboratories and offices striving toward a remedy that tangibly slows cognitive decline. My own team of clinicians and scientists is supported in our work by the Alzheimer's Foundation of America (https://alzfdn.org/), an organization that is consistently ahead of the curve and has the foresight to fund innovative science that would otherwise be overlooked by pharmaceutical companies. Cutting edge technologies involving proteomics and transcriptomics give researchers a constant flow of new information about the brain and I believe that we will find efficacious therapies for AD. It is even possible that amyloid targeting antibodies might be useful as an adjunct treatment to clear away proteinaceous debris once we get moving down a fruitful path. I urge the pharmaceutical companies to consider taking this journey with all of us so that we can get there faster and sooner. The world is waiting.

References

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