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Diving into the Debate Surrounding Aducanumab for Alzheimer's

Dr. Lisk:
The FDA's recent approval of aducanumab for the treatment of Alzheimer's disease has been met with a controversial response. So what do we need to know about this new drug and its potential to treat the progressive neurological disorder?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Jerome Lisk. And joining me to talk about the recent approval of aducanumab is Dr. Peter Whitehouse, Professor of Neurology at Case Western Reserve University. He is also the co-author *of American Dementia: Brain Health in an Unhealthy Society*.

Dr. Whitehouse, welcome to the program.

Dr. Whitehouse:
Great to be with you Dr. Lisk. Thank you.

Dr. Lisk:
Okay, so let's start with some background. Dr. Whitehouse, can you tell us a bit about how aducanumab works in regards to treating Alzheimer's disease?

Dr. Whitehouse:
So that's a very fundamental question because the first thing is, does it work? And that's what all the controversy has been. Studies of aducanumab were stopped because the company actually did a futility analysis and decided to stop the development, but they eventually got it approved through a mechanism at the FDA called Accelerated Approval, which only requires biomarker evidence, and in the case of aducanumab, a monoclonal antibody against amyloid, that was PET amyloid imaging. That is supposed to be reasonably connected to clinical outcomes, but that's where the controversy has been. To my mind it hasn't been proved that this particular biomarker warranted accelerated approval. The meta-analysis shows that it's just not connected clinically adequately yet.

Dr. Lisk:
And so if we zero in on its approval and what clinical trials were conducted to investigate this treatment option, what did they find? And tell us about the neuropsychological test as well.

Dr. Whitehouse:
So there were a variety of primary and secondary outcome measures that were used in the study. A clinicians rating scale called the CDR was one of the primary measures where they found a signal, shall we say, but the FDA statisticians basically rejected that there was any meaningful outcome on either that measure or other neuropsychological measures that were used that were more objective psychological tests, so that, in fact, is why this is controversial. These things were determined by the statisticians by three advisory committee members who resigned from the committee after essentially a unanimous vote with one person abstaining to say this did not meet clinical standards for approval on neuropsychological testing.

Dr. Lisk:
So now the FDA approved aducanumab using Accelerated Approval pathway. What else can you tell us about that, especially how that has impacted the neurological community and the response of the neurologists in the community?

Dr. Whitehouse:
Well with the exception of neurologists that in my mind are consultants to Biogen and have been working with the company, I have been proud of the neurology field, like the leadership of the American Academy of Neurology, who have raised serious concerns about the approval of this drug. And I would say, though it's hard to assess them in a kind of rigorous scientific way, when neurologists have been polled, most of them agree that this drug is not ready for clinical use.

The FDA approved the drug, but the controversy is that CMS, the people who are responsible for paying for aducanumab, have decided only to pay for it in the context of clinical trials, which will severely restrict its use—I think appropriately because we need more scientific data. So Accelerated Approval is based on a biomarker that's unvalidated, without adequate clinical data. And, by the way, there's also serious concern about safety issues. Up to 40% of patients on the drug have something called ARIA, amyloid-related imaging abnormalities, which include edema (swelling) and microhemorrhages. And when you take a drug out of the restrictive populations that are involved in trials and move it into larger-scale clinical practice, those safety issues may become a great concern. So we've got not enough evidence for clinical efficacy, and we've got safety issues.

Dr. Lisk:
So now, before we close, Dr. Whitehouse, what else would you like to add about the controversy surrounding this recent approval?

Dr. Whitehouse:
So I think the important thing to emphasize is not only neurologists who have such an important responsibility for educating their patients about these issues, but other physicians—geriatricians, for example—have come out essentially against this approval and are supporting the idea that we shouldn't pay for it until we have more data. Also, not only CMS, but private payers, Blue Cross Blue Shield, the Cleveland Clinic Health System and, Mount Sinai in New York, they have all said this is not ready for patients yet outside of clinical trials, so this is a rather forceful response.

Dr. Lisk:
But as that brings us to the end of today's program, I want to thank my guest, Dr. Peter Whitehouse, for sharing his insights. Dr. Whitehouse, it was a pleasure speaking with you today.

Dr. Whitehouse:
Likewise, Dr. Lisk.

Dr. Lisk:
For ReachMD, I'm Dr. Jerome Lisk. To access this and other episodes in our series, visit reachmd.com/neurofrontiers, where you can Be Part of the Knowledge.