Prescribing Aducanumab in the Face of Meager Efficacy and Real Risks

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The US Food and Drug Administration (FDA) approved the drug aducanumab on June 7, 2021, using an accelerated approval mechanism, based on evidence that aducanumab reduced brain amyloid-β peptide (Aβ)\(^1\). The FDA press release stated that the effect on the surrogate endpoint “is reasonably likely to predict a clinical benefit to patients…” at some point in the future. As clinical neurologists, we should understand the evidence for this approval and whether this justifies prescribing this medication.

The saga of aducanumab’s journey is convoluted\(^2\)\(^-\)4. Two phase III studies were initiated in August 2015. They were constructed and executed in an identical manner. In March 2017, the sponsor revised the protocol to allow all participants assigned to the high dose arm to receive 10 mg/kg. The sponsor conducted a pre-planned futility analysis which led to termination of both studies in March 2019. Three months later, in a surprise press release, the company stated that subsequent analyses with another three months of data led them to conclude that there was a sufficient clinical efficacy signal to pursue a new drug application. In follow-up post hoc analyses conducted by the sponsor, one trial (“EMERGE” or “302”) showed statistically significant effects in the high dose group on several clinical outcome measures while the other study (“ENGAGE” or “301”) showed no benefits\(^2\)\(^,\)3\(^,\)5\(^,\)6.

We as neurologists need a strategy to advise our patients in this unusual situation where the drug was approved without evidence of consistent clinical benefits. Based on the prescribing information\(^7\), the sponsor shows data from only the positive trial and fails to provide the negative trial’s cognitive and functional outcomes. Neurologists should have access to all of the relevant data in these clinical trials; however, they will have to go elsewhere to find it\(^2\)\(^,\)3\(^,\)5\(^,\)6. Even choosing to focus on the one trial with the favorable outcome in the high-dose group and ignoring the negative trial, the clinical benefits are decidedly small. The drug never produced substantial improvements. The clinical benefit amounted to about 3 months’ worth of delay in decline over a year (annualized Clinical Dementia Rating Scale “sum of boxes” 0.26 rating points reduction in decline with the high-dose aducanumab in the setting of 1.17 points annualized decline in the placebo group). Because our field has not established what constitutes clinical meaningfulness, this benefit could be perceived as having value by some patients and their families. However, this range of delay and progression is well within the untreated variability of groups of patients with mild cognitive impairment (MCI) or dementia due to Alzheimer Disease (AD)\(^8\). The negative trial, which cannot be brushed under the rug, raises questions about the reliability and reproducibility of any such claimed benefits. The sponsor’s presentation at the FDA hearing on November 6, 2020 proposed several post hoc explanations to account for the negative results; however, subjecting the positive trial to post hoc analyses introduced substantial bias and raised serious questions about dose effects and effects on subgroups, as pointed out by the FDA’s statistician\(^9\). Combining the results from the two trials found no statistically significant clinical benefit for high-dose aducanumab\(^6\). As part of this accelerated approval, the FDA requires Biogen to conduct another prospective clinical trial over the next nine years to determine if this drug produces clinical benefit.

The FDA focused on an alternative endpoint to justify accelerated approval of aducanumab. Rather than relying on a failed clinical endpoint, the FDA pointed out that the drug lowered brain Aβ, using this biomarker as a surrogate endpoint. A surrogate endpoint is reasonable if it predicts clinical benefit. However, no data from either trial or any other source indicates that lowering brain Aβ provides clinical benefit to individuals with AD or when such benefit would occur, if it does. In fact, over the 18-month clinical trials with aducanumab, the FDA implicitly acknowledges no consistent clinical benefit occurred. Several studies demonstrated that lowering Aβ in the brain by inhibition of beta- or gamma-secretases made
patients cognitively worse\textsuperscript{10}. Further, the change in cognitive performance in this study did not correlate with the reductions in brain Aβ, as analyzed the FDA’s own statistician. In the cardiovascular world, there are many examples of claims based on “sure-thing” biomarker changes that failed to predict eventual clinical benefits\textsuperscript{11}. Nevertheless, without evidence lowering Aβ can only hope to be disease-modifying.

Neurologists must also consider the risks, especially in light of the low potential for benefit. Infusion of the recommended monthly doses of aducanumab comes with safety concerns, especially in the form of amyloid related imaging abnormalities (ARIA) — edema or hemorrhage. With a rate of 40\%, and higher in apolipoprotein E4 (APOE e4) carriers\textsuperscript{5}, safety monitoring must be integrated into management. Patients must be able to undergo magnetic resonance imaging (MRI) scans and APOE genotyping for safety reasons. Skilled neuroradiology is also a necessity.

With the above caveats, neurologists then need to determine which patients may be appropriate for aducanumab. The prescribing information\textsuperscript{7} states that the drug is indicated “for the treatment of Alzheimer’s disease (AD).” We believe this statement means that suitable patients have the biology of AD, namely elevated brain Aβ and elevated tau. Further, the prescribing information states that the drug is “approved ... based on reduction in amyloid beta plaques observed in patients treated with the drug”\textsuperscript{7}. We take that to mean that its uses in clinical practice should parallel the clinical trials, namely patients with MCI and mild dementia due to AD with biomarker evidence of elevated brain Aβ. No evidence supports using aducanumab in more advanced patients. While there might be a hypothetical basis for treating milder patients, such an approach is also not justified by evidence. There is no evidence for treating patients whose cognitive disorder is jointly attributed to AD and another etiology. And, because aducanumab’s target is elevated brain Aβ, neurologists must have the available technology to verify that a candidate for aducanumab has elevated brain Aβ. Clinical diagnoses alone are insufficient to verify elevated Aβ.

Aducanumab’s approval raises expectations for treatments for patients with symptomatic AD. On the one hand, neurologists want to offer hope. Yet, aducanumab’s benefits are meager, if even present\textsuperscript{12} and there are non-trivial risks of side effects. These issues place a substantial burden on neurologists to take the time and effort to counsel patients and families on expectations for aducanumab treatment. Neurologists will have to manage therapeutic perceptions by presenting their patients and families with unbiased information about the benefits and risks. This is even more challenging as no peer reviewed publication has yet appeared.

References

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