International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 02 Issue 08 August 2022

Page No: 785-786

DOI: https://doi.org/10.47191/ijmscrs/v2-i8-12, Impact Factor: 5.365

Aducanumab Opinion

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ABSTRACT

Aducanumab (brand name *Aduhelm*) is the first FDA-approved, pharmacologic treatment for Alzheimer's disease (AD) but many uncertainties remain regarding both efficacy and safety. Of paramount concern are associated adverse effects including cerebral edema and hemorrhage which prompted a post-approval study. Aside from safety concerns, withdrawal from the market may occur if it fails to demonstrate efficacy as described in pre-approval reports.

ARTICLE DETAILS

Published On:
15 August 2022
Available on:
https://ijmscr.org/

Aducanumab for Treatment of Alzheimer's requires Further Research

The alleged efficacy of aducanumab is not supported by observable clinical benefits and has associated adverse effects of cerebral edema and hemorrhage. [1] Therefore, the drug should not be available to the public until proof of functional improvement and safety are demonstrated.

DISCUSSION

AD affects roughly 6.2 million Americans. [2] The defining pathophysiologic feature of AD is the accumulation of cerebral amyloid beta plaques. Amyloid beta is a pathologic protein known to damage communication between brain cells, leading to their eventual death. Clinically, this manifests as progressive cognitive decline leading to a vegetative state. Aducanumab is a monoclonal antibody that reduces the accumulation of cerebral amyloid beta plaques. The theory is that reduced accumulation of these sticky plaques should afford improvement in cognitive function and quality of life. [3]

While initially touted as a promising advance in AD treatment, the drug failed to demonstrate statistically significant clinical benefit in one of two phases of a 3-phase trial. Inclusion in the trial required a mini-mental state exam (MMSE) score ≥ 24 (mild disease) and a positive PET scan for amyloid. Patients with TIA, stroke or brain hemorrhage were excluded. Approximately 35% of patients treated with aducanumab developed cerebral edema and/or hemorrhage during treatment, and 10% withdrew due to the side effects of headaches, confusion, nausea, or concerns regarding brain imaging abnormalities. Its former advisory panel resigned after expressing concerns surrounding efficacy; they argued that the trial data failed to show clinical benefit. Dunn et al. agree that the drug's clinical effectiveness has not yet been established. Although neuropsychological testing showed a modest improvement in cognitive function for some patients, this was not reflected in the surveys completed by caregivers, the majority of which perceived no improvement. [4] According to data analysis performed by the ICER (Institute for Clinical and Economic Review), it appears that the FDA downplayed its responsibility in reviewing and validating drug efficacy. The primary and secondary outcomes of future studies should be focused on improved cognitive function and quality of life rather than the largely arbitrary scoring and assessment obtained by neuropsychological testing.

While aducanumab has been shown to reduce amyloid burden [5], the degree of amyloid burden does not necessarily correlate with AD severity (i.e., a very high burden can be found in a patient with mild AD). Although the manufacturer-led study is ongoing, independent researchers must continue to be involved in parallel to ensure that patient safety remains the priority. Studies should also strive to establish if the potential benefits of improved performance in ADLs outweigh the potential risks associated with administration. [1] Further, the approval study was based on patients with mild dementia due to AD. [5] It remains to be determined if aducanumab is safe or effective in cases of moderate or severe dementia due to AD.

CONCLUSION

Aducanumab is the first FDA-approved drug for AD since 2003 and made it to market through the accelerated approval

pathway. It should remain off the market until there is valid and reliable proof of both efficacy and safet.

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