Journal of Pharmacoeconomics and Pharmaceutical Management

Journal homepage: http://jppm.tums.ac.ir

Letter to Editor

Accelerated Approval of Highly Expensive Disease-modifying Agents: Lessons Learned From the Aducanumab Approval

Santenna Chenchula[1*], Padmavathi R.[2]

1. Department of Pharmacology, All India Institute of Medical Science, Mangalagiri, India.
2. Department of Medicine, Junior Resident, SVS Medical College and Hospital, Telangana,India.

Use your device to scan and read the article online

Citation Chenchula S, Padmavathi R. Accelerated Approval of Highly Expensive Disease-modifying Agents: Lessons Learned From the Aducanumab Approval Journal of Pharmacoeconomics and Pharmaceutical Management. 2022; 8(1-2):1-4.

Running Title Accelarated Approval of High Cost Aducanumab

Article info:
Received: 25.01.2022
Revised: 01.03.2022
Accepted: 18.03.2022

ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease and the most common cause of dementia affecting millions of people yearly. On June 7, 2021, the U.S FDA granted accelerated approval to highly expensive Aducanumab (Aduhelm), the first-ever disease-modifying drug for the treatment of AD based on its efficacy in reducing Amyloid-beta (Aβ) plaques in the brain. A systematic search of the clinical studies available on the newly approved disease-modifying AD drug, aducanumab was done. Aducanumab was investigated in two Phase-3 placebo-controlled trials (EMERGE: 1638 and ENGAGE: 1647) for its anti-Alzheimer efficacy, in patients with mild AD or mild cognitive impairment due to AD. Findings from both studies revealed no significant changes between the two groups in both the trials, except in trial EMERGE, in which subjects who had received high-dose aducanumab demonstrated a smaller clinical decline from baseline compared to those treated with placebo i.e., 22 % relative reduction in the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB) at week 78. Further, nearly 40% of participants showed Amyloid-Related Imaging Abnormalities (35%) (ARIA), including edema and microhaemorrhage (ARIA-E and ARIA-H).Those pharmaceutical agents approved based upon surrogate bio-markers fail to show any clinical efficacy against to symptoms of patients, in spite of high cost and severe adverse events. Therefore any pharmaceutical agents must be approved only based upon evidence from the confirmatory clinical trials . Clinicians also should be vigilant over any newly approved medications over their clinical evidence rather than believing their efficacy and safety based upon decision of approval bodies, especially the drug like aducanumab.

*** Corresponding Author:**
Santenna Chenchula, PhD.
Address: *Department of Pharmacology, All India Institute of Medical Science, Mangalagiri, India.*
E-mail: *santen7@gmail.com.*

Dear Editor

The US Food and Drug Administration (FDA) has developed the accelerated approval process for earlier approval of drugs that treat serious conditions and fill an unmet medical needs based on a surrogate endpoint that is "reasonably likely to predict clinical benefit to patients" [1]. As of 2020, around 50 million people were suffering from Alzheimer's disease (AD) worldwide, of whom 6.2 million people were from the USA [2]. Currently, cholinesterase inhibitors, N-Methyl-D-Aspartate (NMDA) receptor antagonists, and antioxidants are available for the treatment of AD. Till today, no disease-modifying medications are available for AD [2]. On June 7, 2021, the US FDA granted accelerated approval to aducanumab (aduhelm), the first-ever disease-modifying drug for the treatment of AD based on its efficacy in reducing Amyloid-beta (Aβ) plaques in the brain, which is likely to benefit patients [3] (Figure 1). Regarding this prejudiced decision by the FDA, three members of the FDA review panel resigned against the committee's recommendation [4].

Aducanumab is a human Immunoglobulin G (IgG1) anti-Aβ monoclonal antibody, which selectively binds to β-amyloid oligomers and fibrils in AD. Adacnumab was investigated for its anti-Alzheimer efficacy, in patients with mild AD or mild cognitive impairment due to AD (Mini-Mental State Examination [MMSE] >24, Clinical Dementia Rating [CDR] score of 0.5, and positive amyloid PET scan) in two Phase-3 placebo-controlled trials (EMERGE: 1638 and ENGAGE: 1647) [5]. Unfortunately, both trials were terminated early by Biogen and Eisai, the manufacturers, due to aducanumab ineffectiveness in decreasing levels of amyloid compared to the placebo after a planned futility analysis, which examined clinical outcomes. Later, the maker of aducanumab demonstrated convincingly that, the drug has efficacy in reducing cognitive decline, based on analyses performed using the previously unavailable data collected, after the decision of termination. However, in the EMERGE trial, subjects who had received high-dose aducanumab demonstrated a smaller clinical decline compared to the baseline than those treated with placebo i.e., a 22 % relative reduction in the CDR-SB at week 78 [5]. The absolute difference of 0.39 is of uncertain clinical significance. Very low statistically significant benefits were found regarding other prespecified secondary outcomes. However, in another ENGAGE trial, the CDR-SB scores were not significant between the two groups [5]. Both Amyloid-β (Aβ) plaques and Neurofibrillary Tangles (NFT) are essential pathophysiological surrogate markers in AD. Prior to this, drugs that decreased Aβ in the brain did not show any clinical efficacy in patients with AD [6].

A surrogate endpoint or marker is a laboratory measurement or physical sign used as a substitute for a clinical endpoint, which measures how a patient feels, functions, or lives longer. In the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) the US FDA has defined legal standards for Drug and Biological Products effectiveness as "substantial evidence" defined in section 505 (d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, based on which it could fairly and responsibly be concluded by such experts that the drug will affect it purports or is represented to have under the conditions

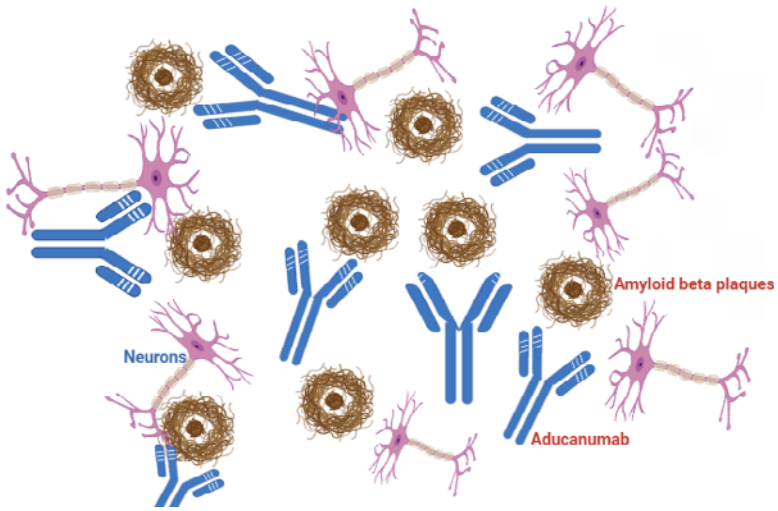

Figure 1. disease-modifying drug for the treatment of AD based on its efficacy in reducing Amyloid-beta (Aβ)

of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" [7]. However, by this definition, it may approve a drug product, which has an effect on some measurements that reflect absolutely no clinical benefit to the patient as long as it can be adequately described in the label, but in reality, the clinical outcome of interest does not correlate with the surrogate marker due to its efficacy only on the course of the disease rather than a reversal of the disease. Hence, changes in levels of surrogate biomarkers are reasonable to use only in the early stages of drug development than at the level of controlled trials for effectiveness in patients. Earlier to this, there are many examples of accelerated approved drugs showing clinical benefit in confirmatory trials in patients [8]

Most importantly, the annual cost of the aducanumab treatment is very high i.e. $56,000 [4]. Until now it is still uncertain whether an insurer will cover this most expensive treatment, including treatment monitoring scans. Most insurers choose not to cover a high-cost drug approved based on the lack of clinical evidence.

In addition, aducanumab has been shown to cause some serious adverse events with the high dose that was used in clinical trials. It was associated with Amyloid-Related Imaging Abnormalities (35%) (ARIA), including edema and microhaemorrhage due to compromised blood-brain barrier, and requires regular MRI brain monitoring during the treatment [2, 4]. In a recent meta-analysis of phase III trials of anti-amyloid drugs, in patients with AD (seventeen studies: n=12,585), no significant clinical improvement was found, but the ARIA increased by large effect size when all drugs were pooled together [6].

High price drugs appear in the market, due to granting approval to a drug without providing any government-funded drug benefits to the drug manufacturers [8]. All the aforementioned challenges create people's skepticism about the approval bodies. To address this challenge of high cost, several policy options need to be modified and implicated by the policymakers. If the drug authorities must approve a drug by the accelerated approval process for any serious life-threatening diseases, due to the unavailability of newer treatments since long duration or any disease-reversing agents, drug approval authorities should reimburse or provide special price negotiation by the government for manufacturing costs until the availability of evidence from the clinical trials. In addition, drug manufacturers can also provide additional concession benefits in the cost of the annual treatment for their approved drug based on the surrogate markers rather than confirmatory evidence in the clinical trials [8].

At present, aducanumab can only be used in patients with amyloid-positive mild cognitive impairment along with close monitoring for adverse effects. Although the presence of great excitement on the faces of patients and family members of AD is acceptable, this must be tempered by many shortcomings, such as paucity in the clinical trials findings, risk of serious adverse effects, and cost of the treatment. Consequences of the accelerated approval of these highly expensive treatments in the current era of restrained resources due to the ongoing pandemic lead to reduced resources available for healthcare that are very essential lifesaving services with strong clinical evidence. Therefore, high-cost therapeutic agents must be approved based on evidence from the confirmatory clinical trials than a biomarker-based accelerated approval process to provide effective therapeutic management. In addition, clinicians should be vigilant over any newly approved medications over their clinical evidence rather than believing their efficacy and safety based upon decision of approval bodies, especially the drug like aducanumab.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization and Writing-original draft: Santenna Chenchula; Writing-review & editing: Padmavathi R.

Conflict of interest

The authors declared no conflict of interest.

References

[1] U.S. Food and Drug Administration. Accelerated Approval Program [Internet]. 2020. [Updated 2020 October 26]. Available from: https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program

[2] No Authors. 2021 Alzheimer's disease facts and figures. Alzheimers Dementia. 2021; 17(3):327-406. [DOI:10.1002/alz.12328] [PMID]

[3] U.S. Food and Drug Administration. FDA grants accelerated approval for Alzheimer's drug [Internet]. 2021 [Updated 2021 June 7]. Available from: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug

[4] Mahase E. Three FDA advisory panel members resign over approval of Alzheimer's drug. BMJ. 2021; 373:n1503. [DOI:10.1136/bmj.n1503] [PMID]

[5] Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer disease: Scientific evidence and regulatory review involving efficacy, safety, and futility. JAMA. 2021; 325(17):1717-8. [DOI:10.1001/jama.2021.3854] [PMID]

[6] Lu L, Zheng X, Wang S, Tang C, Zhang Y, Yao G, et al. Anti-Aβ agents for mild to moderate Alzheimer's disease: Systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2020; 91(12):1316-24. [DOI:10.1136/jnnp-2020-323497] [PMID]

[7] US Department of Health and Human Services, CDER, CBER. Guidance for Industry: Fast track drug development programs- designation, development, and application review. Food and Drug Administration, 2006. http://www.msk.nclinnovations.org/medregulations/v1/html/Guidance/Guidance_Fast%20Track%20Development.pdf

[8] Gellad WF, Kesselheim AS. Accelerated approval and expensive drugs: A challenging combination. N Engl J Med. 2017; 376(21):2001-4. [DOI:10.1056/NEJMp1700446] [PMID]