Aducanumab for Alzheimer's Disease: A Regulatory Perspective

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Received: 23-Jan-2024; Manuscript No. mrcs-24-99808; **Editor assigned**: 24-Jan-2024, Pre QC No. mrcs-24-99808 (PQ); **Reviewed**: 3-Feb-2024, QC No mrcs-24-99808 (Q); **Revised:** 5-Feb-2024, Manuscript No. mrcs- 24-99808 (R); **Published:** 10-Feb-2024. 09(01), 001-003

Abstract

Background: The most common reason for dementia, which is marked by a continuous decline in mental, behavioral, and social skills and reduces a person's capacity for independent functioning though the uncertainties remain regarding the precise etiology of Alzheimer's. There are 3 stages of the disease- Mild, Moderate, Severe. Aducanumab is a newly developed drug approved for the treatment of Alzheimer's. In June 2021, the FDA approved aducanumab for the treatment of Alzheimer's. This drug was approved on the basis of FDA's accelerated Pathway.

Objective:The study aims to determined the regulatory perspective in development of drug, challenges faced by FDA in drug approval and the clinical trials results.

Methods:Information for this review was gathered from published works as well as publicly available documents from the government and regulatory agencies. Search terms related to aducanumab, immunotherapy, antibodies, anti-beta-amyloid therapy, memory loss, treatment and mild cognitive impairment. Using platforms like Web of Science, Medline, Google Scholar, Pubmed, FDA websites, and the manufacturer's website, clinical trials, reviews, and updates on aducanumab in AD patients have been published.

Results:These preliminary studies of the drug demonstrate its efficacy in decline in amyloid plaque from the brain as well as its potential advantage in delaying cognitive decline in Alzheimer's patients.

Following the phase 1B (PRIME) trial's encouraging findings, two 18-month phase III ENGAGE and EMERGE. The ADCS-ADL scale also revealed a 40% slower rate of functional deterioration as compared to the placebo group, while the Neuropsychiatric Inventory (NPI) test revealed an 87% decrease in behavioral changes from baseline scores, particularly in the EMERGE high-dose group. The ENGAGE study, on the other hand, failed to demonstrate any dose-dependent advantage of pharmacological therapy over placebo. The drug is still in the phase 4 trial.

Conclusion:Aducanumab regularly and strongly demonstrated a dose- and time-dependent decrease in the amount of amyloid plaques in the brain. This indication has been given accelerated approval. The controversies surrounding the FDA's approval of aducanumab, however, the issues raised by the FDA's approval of aducanumab significance further investigation in order to restore public confidence in the review process, not only for aducanumab's potential promise but, more importantly, for the upcoming formation of desperately needed disease-modifying therapies for this emerging conditions.

Keywords: Alzheimer's disease ● Aducanum● Abamyloid plaques

Introduction

Three histo-pathologic changes in the brain are associated with Alzheimer's disease (AD): 1) Cerebral atrophy linked to the deterioration and degeneration of nerve cells; (2) the formation of senile plaques made up of accumulated amyloid-ß (Af) protein; (3) aberrant tau protein aggregation and phosphorylation; which results in the formation of neurofibrillary tangles. In the United States, 5.8 million persons aged sixty and older have Alzheimer's disease. 80% of them are 75 or older. Between 60% and 70% of the estimated 50 million dementia sufferers globally are thought to have Alzheimer's disease. The brain shrinks and brain cells die as a result of the neurologic degenerative disorder known as Alzheimer's disease. The most common reason for dementia, which is marked by a continuous decline in mental, behavioural, and social skills and reduces a person's capacity for independent functioning Though the uncertainties remain regarding the precise etiology of Alzheimer's disease [1]. However, brain proteins fundamentally malfunction, which impairs the work of brain cells (neurons) and triggers off from a series of harmful events. Damaged neurons lose connections with other neurons and finally die. According to scientists, Alzheimer's disease affects the brain over time and is typically brought on by a combination of hereditary, environmental, and lifestyle factors for most people [2]

There are 3 stages of the disease- Mild, Moderate, Severe. The symptoms associated with the Alzheimer's disease-related memory loss persists and gets worse, making it difficult to carry out daily tasks at home or at work. Frequently state and ask the same questions, forget meetings, activities. Apart from this, concentration and thinking problems, especially when it comes to abstract ideas like numbers. Multitasking is very challenging especially in making decisions and judgments, planning and carrying out routine activities. The main risk factor associated with the disease are age, family history, and genetics moreover, down syndrome, minimal brain impairment and head injury are other some risk factors. biological mechanisms including eating, posture, and bladder and bowel regulation begin to be affected by abnormalities in the structure of the brain as the symptoms of Alzheimer's disease progress. Aspiration of food or liquid into the lungs, flu, pneumonia, falls, and fractures can also occur as the complications of the disease. For diagnosis purpose physical and neurological examination, laboratory tests, and brain imaging such as MRI and CT scans are performed. Additionally, PT scans are used for diagnosis the progression of the disease. Treatment include Cholinesterase inhibitors like (donepezil, glutamine and rivastigmine). Memantine.

Aducanumab

Aduhelm is a ground-breaking medication approved for the treatment of Alzheimer's. In June 2021, the FDA approved aducanumab for the treatment of Alzheimer's. It is the first brand-new Alzheimer's drug to be licensed since 2003 and the first to concentrate on the fundamental pathophysiology of thecondition. It is a monoclonal antibody against amyloid beta.The accumul ation of amyloid beta plaques in the brain is one defining pathophysiological characteristic of Alzheimer's disease. Based on evidence from clinical trials Aducanumab is formed to target and eliminate particular types of beta-amyloid that build up into plaques and may be a factor in cell death and tissue loss in regions of the brain that are crucial for memory, thinking, learning, and behaviour. These regions are those where plaques are particularly important because they are where these functions are performed. Auranumab reduces the quantity of beta-amyloid produced by the brain, which is still produced. Other brain functions may perform better as a result of its removal. showing ADUHELM's influence on reducing amyloid beta plaques, a surrogate biomarker with a reasonable likelihood of predicting treatment benefit, in this case a decrease in clinical decline, the

medication has been given fast approval from FDA. Dosage Forms & Strengths available is 100mg/mL IV. IV infusions are given at intervals of at least 21 days, every four weeks. Dosing titration schedule for 1 to 2 infusions is 1 mg/kg IV q4Weeks, then for 3 to 4 infusions 3 mg/kg IV every four weeks, 5–6 infusions IV 6 mg/kg and 7th infusions and later 10 mg/kg IV, every four weeks are there. The smaller oligopeptides and amino acids that make up aducanumab are excreted [3].The drug's terminal half-life and average clearance are 24.8 days and 0.0159 L/h, respectively. Age, sex, body weight, and ethnicity don't seem to have any discernible effects on how much of the drug is exposed to in humans [4,5].

Material and methods

Information for this review was gathered from published works as well as publicly available documents from the government and regulatory agencies. Search terms related to aducanumab, immunotherapy, antibodies, anti-beta-amyloid therapy, memory loss, treatment and mild cognitive impairment. Using search engines like Google Scholar, Web of Science, Pubmed, FDA websites, and the manufacturer's website, clinical trials, reviews, and updates on aducanumab in AD patients have been published.

Results

Preclinical and Phase 1

Both the pre-clinical animal model and the Phase 1b placebo-controlled trial with 165 prodromal and mild AD patients (n=165) showed that aducanumab decreased amyloid-beta levels in the brain, and that the drop was dose-dependent. Clinical decline in AD patients might be avoided by removing the amyloid-beta plaque, which has been linked to the disease's onset. [6].These preliminary studies of the drug demonstrate its efficacy in clearing amyloid plaque from the brain as well as its potential advantage in delaying cognitive decline in Alzheimer's patients. Additionally, preliminary findings from the Phase 1b research showed a dose- and time-dependent slowing of clinical decline as indicated by the Clinical Dementia Rating-Sum of Boxes and on the MMSE (Mini Mental State Examination Score) [7].

Phase 2

The EVOLVE phase II trial (NCT03639987) provides the safety and effects in patients with asymptomatic ARIA who also had mild cognitive impairment (MCI) associated mild dementia. The trial also intended to assess ARIA from an imaging and clinical standpoint, as well as the safety, tolerability, pharmacokinetics, and immunogenicity of aducanumab. These studies was latter terminated.

Phase 3

Following the phase 1B (PRIME) trial's encouraging findings, two 18-month phase III ENGAGE and EMERGE (EMERGE NCT02484547 and ENGAGE (NCT02477800) trials with identical designs were carried out to determine whether clearing -amyloid plaques affected how slowly patients with decline in memory and thinking. Patients in both trials ranged in age from 70 to 80 years. The effectiveness of the medicine in preventing the disease from progressing was assessed in the experiment using a clinical dementia rating scale. The EMERGE trial demonstrated a benefit with a greater dose, according to a reanalysis of bigger data with 3285 patients. Adjusted mean clinical dementia rating scores improved by 22% in EMERGE trial patients receiving high doses of aducanumab. Additionally, an 84% decrease in caregiver discomfort was noted. The ADCS- ADL scale also revealed a 40% slower rate of functional deterioration as compared to the placebo group, while the Neuropsychiatric Inventory (NPI) test revealed an 87% decrease in behavioral changes from baseline scores, particularly in the EMERGE high-dose group. The ENGAGE study, on the other hand, failed to demonstrate any dose-dependent advantage of pharmacological therapy over placebo. Less participants in the ENGAGE study who received greater doses of aducanumab can be reason for the differences. For 2,400 former aducanumab trial participants, Biogen announced a Phase 3b open-label study on January 27, 2020. Participants would receive monthly injections of 10 mg/kg for two years. Only safety and tolerability parameters are listed as the trial's key endpoints. known as EMBARK. [8].

Phase 4

The research, which will be a global, placebo-controlled trial with a primary clinical outcome at 18 months following therapy beginning, is a post-marketing requirement of the FDA's expedited approval and aims to enroll more than 1,300 early Alzheimer's disease patients. The study's primary completion date is anticipated to occur four years after it starts, based on participation rates from earlier Phase 3 trials with ADUHELM. A long-term extension of the experiment will be used to gather data on the effects of the treatment for a period of up to 48 months [8].

Discussion

For medications that cure serious illnesses and meet an unmet medical need, the FDA established the Accelerated Approval Program. A substitute or intermediary clinical endpoint serves as the basis for approval (in this case reduction of amyloid plaque in the brain). If a marker—such as a laboratory value, radiographic image, physical sign, or other measure—is thought to predict clinical benefit but is not a clinical benefit measure in and of itself, it is referred to as a surrogate endpoint. The amount of time needed to obtain FDA approval can be significantly reduced by using a surrogate endpoint [9].

The drug was given to patients with mild dementia or moderate cognitive impairment. There is no information on the effectiveness or safety of initiating treatment at an earlier or later stage of the illness than was assessed. Aducanumab regularly and strongly demonstrated a dose- and time- dependent decrease in the amount of amyloid plaques in the brain. Clinical decline is anticipated to slow down with the reduction in amyloid plaque. This indication has been given accelerated approval. Verification of clinical benefit in confirmatory trials may be necessary for this indication's continued approval. In circumstances when the statistics are not clear-cut, Regulatory bodies proceeded as usual when making conclusions. They thoroughly studied the clinical trial results, asked the Peripheral and Central Nervous System Drugs Advisory Committee for advice, heard from the patient population, and analyzed all pertinent data. The FDA has emphasized that in making its own determination under the fast approval pathway, it took into account both the urgency and the expectation of a significant advantage above existing symptomatic medicines that are based on a strategy for illness modification. With the disclaimer that the FDA has regulatory resources available to it to remove the drug from the market in the event that the confirmatory trials are unable to confirm the efficacy/clinical benefit of the drug, the marketing authorization holder (MAH) will be required to carry out a post-approval study (phase 4 confirmatory trial) lasting up to four to nine years to determine the clinical benefit. Before forming a judgment, regulators around the world thoroughly examine the benefit-risk profile of a pharmaceutical product [10].

Conclusion

Related this evidence reported and the specific distribution by age of rare pericarditys or CNS thrombosys After some C.O.V.I.D.-19 vaccination Is crucial to more deeply investigate if there are relationship with graphene impurities (if present) and the wireless radiation or not. The same to verify if this effect can produce pathological event in significative clinical way. Even if the protrombotic and proinflamatory effect of the S.A.R.S. cov-2 spike protein are cleary reported by many scientific database and the effect played by various wireless radiation are studied using various models it is relevant to verify also if a cumulative effect can act on a ptahological common event. The same it is crucial verify if Garphene presence with its electrical conductivity can increase the effect played by electromagnetic field on *SPIKE protein-ace2 rec*. (various independent researcher reported evidence or in vials of vaccine or in blood of vaccinated).

Even if in the various countries C.O.V.I.D.-19 vaccine Spike protein based have been approved by regulatory agency The report of some rare adverse event in subpopulation or limitation of other vaccine according the age class require a more deeply investigation to find if present relationship of interest (Every year various approved drugs are recalled by authorities due by safety motivations) because toxicity of S.A.R.S. cov-2 virus spike protein can produce clots, pericarditys or other pathologic event . It is of interest to evaluate some additional co- factor in the case of C.O.V.I.D.-19 vaccine spike based. What happen in presence of graphene derivates and what happen under determinate condition of external electro-magnetic filed and what effect is played by various electromagnetic field intensity applied or by the time of application?

Related this topic it is interesting to observe that there are no or few literature about the effepct played by the combination of spike protein – ace and graphene under various grade of electro- magnetic field. “It has been theoretically predicted and experimentally demonstrated that static and time-dependent electric fields (EFs) are capable of inducing conformational changes or even irreversible damage in proteins” and “ACE2 binding to S.A.R.S.-CoV-2 strictly requires the up conformation of R.B.D.” “Electric fields are able to induce global conformational changes in the spike glycoprotein, affecting the stability of folding states”. (As written by Claudia R. Arbeitman et al) So The intensity and duration of the link between SPIKE

and ACE is influenced by electric fields (maximum or minimum effect according the intensity of interference).
The rare effect observed for some mR.N.A. Vaccine like pericarditis in young are currently reported in scientific database, the same the procoagulant effect but because there is a variability in this effect it can be relevant observe the environment around the patient body and the real composition of the vaccine vials.
Various independent reseacher finded graphene derivates in some vials of C.O.V.I.D.-19 vaccine and the same other reported this substantie in blood of vaccinated because electro-magentic field can modify the electrical charge of various molecule it is crucial for the author of this work to invesigate deeply the cumulative affect played by this three independent factor (primary or secondary) in the development of adverse event.
Mainly related the intensity of this relationship and during a wide windows of time. Even if the aggressivity of phenomena is not really high the persistence during time can produce pathological effect.

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Cite this article: Shah K. Aducanumab for Alzheimer's disease: *A regulatory perspective* 2024, 9(1), 001-003