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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Aducanumab. [Updated 2021 Jun 25].
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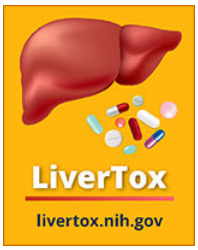

Aducanumab

Updated: June 25, 2021.

OVERVIEW

Introduction

Aducanumab is a human monoclonal antibody to amyloid β which has been approved for use in Alzheimer disease. Aducanumab is associated with a minimal rate of serum aminotransferase elevations during therapy and has not been linked to instances of clinically apparent liver injury.

Background

Aducanumab (a" due can' ue mab) is a human monoclonal IgG1 antibody directed against amyloid β which was developed as therapy for Alzheimer disease, based upon the theory that the dementia and neurological decline in Alzheimer disease is caused by accumulation of amyloid β oligomers and fibrils in the frontal lobes of the brain. Studies in animal models and in humans demonstrated that the monoclonal antibody causes a decrease in amyloid β accumulation as shown by advanced imaging techniques. Whether this results in improvement in dementia or lessens clinical progression of disease has not been shown. Aducanumab was evaluated in two large, randomized double-blind controlled trials in more than 3200 patients with early stages of Alzheimer disease and evidence of amyloid β plaques accumulation. Clinical responses were minimal although analysis of a subgroup of patients who received the highest dose in one of the two trials showed evidence of a significant improvement in the clinical dementia rating scale. Because of the severity of Alzheimer disease, the lack of any therapy that slows the progression of disease and the firm biologic basis for possible efficacy of aducanumab, it was given provisional approval in the United States in 2021 as therapy in patients with Alzheimer disease who have evidence of progression and presence of amyloid β plaques. The provisional approval requires conduct of a phase IV study to further evaluate and confirm its safety and efficacy. Aducanumab is available in single dose vials of 170 in 1.7 mL and 300 mg in 3 mL (100 mg/mL) under the brand name Aduhelm. The recommended dose is 10 mg per kilogram body weight administered intravenously (over approximately 1 hour) every 4 weeks with regularly scheduled evaluations for efficacy. Common side effects include infusion reactions, headache, falls, and amyloid related imaging abnormalities such as edema, hemorrhage and hemosiderin deposition. Uncommon, potentially severe adverse reactions include hypersensitivity reactions.

Hepatotoxicity

Serum aminotransferase elevations were infrequent in the large controlled trials of aducanumab in Alzheimer disease. The elevations were generally mild-to-moderate in severity, transient and asymptomatic. In the preregistration trials there were no instances of clinically apparent liver injury or severe hepatic adverse events attributed to aducanumab. Clinical use outside of randomized controlled trials has been limited so far.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

The possible mechanisms by which aducanumab might cause liver injury are unclear. Monoclonal antibodies and immunoglobulins are generally taken up and metabolized intracellularly to short peptides and amino acids. There is no evidence to suggest that inhibition of amyloid β accumulation or increase in its clearance would trigger liver injury or autoimmune liver conditions.

Drug Class: Monoclonal Antibodies, Alzheimer Disease Agents

Other Alzheimer Monoclonal Antibodies: Lecanemab

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Aducanumab – Aduhelm®

DRUG CLASS

Alzheimer Disease Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Aducanumab	1384260-65-4	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 25 June 2021

Roberson ED. Alzheimer Disease. Treatment of central nervous system degenerative disorders. In, Brunton LL, Hilal-Danan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 333-5.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf

(Multidisciplinary FDA review of aducanumab in support of its approval for use in Alzheimer disease in the US with discussion of safety, mentions that the laboratory findings from the prelicensure studies "did not identify any clinically meaningful change in patients treated with aducanumab").

Ratner M. Biogen's early Alzheimer's data raise hopes, some eyebrows. Nat Biotechnol. 2015;33:438. PubMed PMID: 25965736.

(News report on release of interim results of a phase 1 study of aducanumab in Alzheimer disease which described decreases in β-amyloid plaques in treated patients as assessed by PET scan, but with no data on clinical efficacy in reversing or slowing progression of dementia; the results were encouraging enough directly go to phase 3 trials of the monoclonal antibody).

Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016;8:595–608. PubMed PMID: 27025652.

(Analysis of the role of amyloid-β in the etiology of Alzheimer disease supported by findings that the dominant mutations in amyloid precursor protein [APP] or the protease that metabolizes presenilin and generates amyloid-β are associated with early onset dementia, suggesting that imbalance of generation and clearance of amyloid-β is the early and perhaps initiating factor in Alzheimer disease, and that monoclonal antibody therapy by increasing clearance might help correct the dyshomeostasis).

Ferrero J, Williams L, Stella H, Leitermann K, Mikulskis A, O'Gorman J, Sevigny J. First-in-human, double-blind, placebo-controlled, single-dose escalation study of aducanumab (BIIB037) in mild-to-moderate Alzheimer's disease. Alzheimers Dement (N Y). 2016;2:169–76. PubMed PMID: 29067304.

(Phase one study of escalating single doses of aducanumab [0.3, 1, 3 10, 20, 30 and 60 mg/kg] vs placebo in 53 patients with mild-to-moderate Alzheimer disease; four receiving the 60 mg/kg dose developed symptomatic amyloid related imaging abnormalities; no mention of ALT elevations or hepatotoxicity).

Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016;537:50–6. PubMed PMID: 27582220.

(Among 165 patients with early Alzheimer disease treated with 1 of 4 doses of aducanumab [1, 3, 6, or 10 mg/kg] or placebo monthly for one year, those treated with the higher doses showed evidence of decrease in brain amyloid-β accumulation and a trend for clinical improvement, but also higher rates of vasogenic edema [37% to 40%] compared with placebo [5%]; ALT elevations arose in 4 of 125 [3.2%] on aducanumab vs none of 40 on placebo).

Hawkes N. Merck ends trial of potential Alzheimer's drug verubecestat. BMJ. 2017;356:j845. PubMed PMID: 28202490.

(News report on the termination of a large randomized controlled trial of verubecestat [a small molecule inhibitor of β site amyloid precursor protein cleaving enzyme 1: BACE-1] because of futility).

Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimers Dement. 2021;17:696–701. PubMed PMID: 33135381.

(In a reanalysis of results from two large controlled trials of aducanumab in early Alzheimer disease, the authors conclude that there was likely a dose related effect on brain amyloid-β plaque accumulation, but the studies did not show evidence of clinical benefit, which calls for a third, adequately powered trial using higher doses and in more extended populations of subjects with Alzheimer disease).

Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer disease: scientific evidence and regulatory review involving efficacy, safety, and futility. JAMA. 2021;325:1717–8. PubMed PMID: 33783469.

(Summary of the conclusions of the FDA advisory committee on aducanumab which were based upon results of two phase III randomized controlled trials in early Alzheimer disease patients, both of which were terminated early after interim analyses indicated futility; but on post-hoc reanalysis, statistically significant benefit was found with the higher dose in one of the 2 trials; because of discrepancies in outcomes in the two trials and only slight clinical benefit achieved in one arm of the 2 studies, the committee recommended that aducanumab not be approved until another trial confirms the efficacy and safety of the high dose regimen).